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Phase II Cancer Prevention Clinical Trials

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Abstract

The development of agents to prevent cancer requires an iterative process of target identification, preclinical testing, and early and late phase clinical trials to establish efficacy and safety. Since phase III definitive efficacy trials with cancer endpoints require a lengthy timeframe and considerable resources for completion, it is critical to first optimize agent delivery and trial design and to determine preliminary efficacy via the conduct of phase II trials. Phase II trials vary considerably in their endpoints, cohorts, and designs due to differences in the process of carcinogenesis and ability to sample tissues across different target organs. The goal of all such trials, however, is to provide evidence of interference with the development of cancer and to identify safety signals that would limit the benefit from interventions.

Introduction

Abundant evidence indicates that invasive cancer can be prevented, or at least significantly delayed, if addressed early enough. Clinical successes include FDA-approved approaches such as breast cancer risk reduction with tamoxifen or raloxifene, cervical cancer prevention with vaccines against human papillomavirus, and reduction in colorectal polyp number in familial adenomatous polyposis.^{1–5} However, with an ever increasing understanding of the molecular events leading to cancer at a variety of target organ sites and an increasing number of potential targets for intervention, it is essential to prioritize agents for drug development. The convincing demonstration of prevention of a disease that occurs only in a portion of the study population requires large clinical trials of lengthy duration. For instance, the STAR and ATBC breast and lung cancer phase III trials required five or more years of treatment of over 19,000 and 29,000 individuals, respectively, to demonstrate 163 and 876 new cases of breast and lung cancer.^{2, 6} It is therefore necessary to ensure that maximal efficacy and safety information is known prior to committing the considerable resources that are required for phase III cancer prevention trials. Phase II preliminary efficacy clinical trials provide critical human data to inform the “go-no go” drug development decision. This review will provide an overview of phase II cancer prevention trial design, including issues inherent to the choice of targets, optimization of risk-benefit ratios, cohort selection, and intermediate endpoint assessment.

Target Selection for Cancer Prevention Trials

The selection of appropriate targets for intervention is the most critical component of the drug development process. Appropriate target selection is based on efficacy assessment as well as

the potential negative effects of impacting the target (as discussed below). Indications of effectiveness fall into several major categories - knowledge of mechanisms, *in vitro* and animal *in vivo* experimental data, epidemiological case-control and cohort studies, and data from clinical trials, either early phase prevention trials or secondary endpoint analysis from trials performed for other indications (reviewed in ref. 7). During each stage of drug development, but particularly at the juncture between preclinical and early clinical trials and then again at the juncture between early phase and definitive phase III clinical trials, it is necessary to review all the available data and to examine it for consistency. The quality and consistency of the available data help determine whether additional data needs to be obtained prior to clinical trials, or if sufficient knowledge is available to make the “go-no go” decision.

Understanding the mechanisms responsible for carcinogenesis at specific target organs is critical to designing the appropriate clinical intervention trials. However, despite the recent logarithmic increases in our knowledge, the detailed mechanisms giving rise to most human cancers are not well worked out. It is becoming clear that cancer represents a multitude of molecular processes with different pathogenetic mechanisms even within the same target organ. For instance, breast cancer classification has moved beyond the simple estrogen receptor-positive and estrogen receptor-negative categories, while a variety of molecular alterations, several of which can be specifically targeted for therapy, are known to lead to lung adenocarcinoma.^{8,9} This molecular complexity suggests that multiple strategies may well be needed to prevent different types of cancers and thus it becomes even more important to identify the individuals at high risk for specific molecular types of cancer.

The more dependent a cell is on a particular pathway for its growth and survival, the more likely that an intervention blocking the pathway will be effective. This is best illustrated by the tyrosine kinase inhibitor imatinib, which inhibits p210^{BCR-ABL} that causes chronic myelogenous leukemia (CML) and also inhibits c-Kit, which is involved in gastrointestinal stromal tumors (GIST) and small cell lung cancer (SCLC).¹⁰⁻¹² In CML, p210^{BCR-ABL} is necessary and sufficient to cause the disease, and imatinib has striking efficacy, especially in the early chronic phase. In fact, chronic CML can be considered a premalignant phase of the leukemic process. However, imatinib's efficacy decreases markedly with advancing disease, such as accelerated phase and blast crisis, both of which are characterized by the accumulation of additional mutations. Similarly, in GIST, c-Kit is mutated and imatinib is again very effective in the tumors with the appropriate mutations. However, in SCLC, although c-Kit is frequently expressed, activating mutations in c-kit exon 11 are not found while a multitude of other mutations in other genes do exist, and imatinib is inactive.¹³ Efficacy in blocking a single pathway only occurs when the cell is critically dependent on that pathway.

Thus, the better one understands the process of carcinogenesis and the molecular basis for the evolution of the neoplastic phenotype, the more likely will one be able to develop interventions to prevent and possibly even reverse neoplastic progression. The efficacy of an agent in preventing cancer will depend on how critical its target is to carcinogenesis (as exemplified by the role of imatinib in CML), whether the agent can be delivered at the time that its target drives the carcinogenic process, and the potency of the intervention. Because different aspects of carcinogenic progression may depend on different molecular abnormalities or signaling pathways, it is important to determine when specific abnormalities should be targeted. For instance, targeting the initial DNA damage from carcinogen exposure in tobacco smoke by blocking carcinogen metabolism may be very effective prior to the acquisition of much DNA damage, but is not likely to be effective once the damage already exists and cells have acquired multiple genetic lesions (e.g., after years of smoking). A priori, there is no reason to theorize that interventions that are effective during some phases of carcinogenesis will be effective during other stages, unless the target has a critical biological role during multiple stages of carcinogenesis. Finally, it is important to remember that phase III cancer prevention trials with

tumor incidence endpoints generally test interventions for only a small number of years, so these trials are, by design, testing intervention efficacy on relatively advanced stages of premalignancy (Figure 1). Consequently, an intervention that blocks early events in carcinogenesis, such as initiating DNA damage events, is highly unlikely to prevent cancer in a trial where the duration of the intervention is 3–5 years. In selecting targets for cancer prevention, the ability to design the appropriate clinical trials to demonstrate efficacy must be considered – if one cannot demonstrate preventive ability within the context of our currently available clinical trials resources (for instance, if the intervention must be delivered prior to all carcinogen exposure), the drug development process is likely to fail.

The Risk-Benefit Balance

The side effect profile of a putative chemopreventive agent is as important as its efficacy, although safety alone is insufficient to justify clinical trials. The main issues to consider regarding the side effect profile of potential chemopreventive drugs are the common minor side effects that are not consequential to general health but may significantly impact quality of life or compliance and uncommon major side effects that threaten an individual's short term or long term well-being and thus potentially substitute another serious disease for cancer.

To be acceptable for cancer prevention, a drug has to be tolerable so that people will be willing to take it for extended periods of time. The level of discomfort that is tolerable varies considerably, depending on the clinical context. For instance, in a chemoprevention trial of anethole dithiolethione (ADT) for the reversion of bronchial dysplasia, NCI common toxicity criteria (CTC) grade 2 side effects (mainly gastrointestinal) resulted in protocol-mandated dose reductions in 45% of participants taking ADT versus 25% taking placebo.¹⁴ While this level of toxicity is quite mild compared with the more severe (grade 3 and 4) toxicities frequently encountered during treatment for metastatic cancer with any of a variety of agents, the clinical context (low short term risk of death and anticipation of lengthy duration of treatment for chemoprevention) is quite different. Even mild toxicities may be bothersome enough to affect quality of life and compliance in the setting of cancer prevention and thus may limit the utility of effective agents.

Although tolerability and impact on quality of life may limit the potential utility of chemopreventive interventions, the rare but serious short and long term side effects are of even greater concern. Several phase III cancer prevention trials, in part due to their placebo-controlled design and long careful follow-up, have demonstrated adverse effects that have limited the uptake of efficacious agents into common medical practice. The NSABP P-1 study of tamoxifen for breast cancer prevention showed an increased risk for the development of endometrial cancer (RR=2.53, 95% CI=1.35–4.97) and an increase in the incidence of stroke, pulmonary embolism and deep-vein thrombosis, all in the context of an impressive 49% decrease in invasive breast cancer.¹ These adverse events were more frequent in women over age 50, with no endometrial cancer occurring in women under 50 years. Nevertheless, despite no significant differences in important adverse events between tamoxifen and placebo in women under 50 years of age, the perception of tamoxifen as being too toxic for prevention persists, and use has been limited even in this age group.

A different clinical situation arose from the identification of significant cardiotoxicity using rofecoxib treatment for the prevention of recurrence of colorectal adenomas. Although associated with a 24% decrease in colorectal adenoma recurrence, extended use of rofecoxib was found to increase the relative risk of thrombotic events such as cardiac events (HR=2.80, 95% CI, 1.44–5.45) and cerebrovascular events (HR=2.32, 95% CI, 0.89–6.74).^{15,16} Rofecoxib was subsequently withdrawn from the market. The initial report indicated that cardiovascular risk did not increase until approximately 18 months after drug use, raising the

intriguing dilemma of how to identify increased risk of common diseases such as cardiovascular events in the elderly that do not occur until later time points and thus are unlikely to be identified in the original drug registration trials of relatively short duration.

It thus becomes clear that the appropriateness of an agent for prevention is dependent not only on tolerability and side effect profile, but also on the cancer risk of the intended cohort and the duration of the intervention. The acceptable level of toxicity and the risk of the cohort for serious disease are directly related – the higher the risk of immediate serious disease, the higher the toxicity that is acceptable for interventions. Since almost all interventions are likely to have some side effects, it is critical to identify the most appropriate high-risk cohorts who stand to benefit the most from interventions. Similarly, tailoring therapies toward those who are most likely to respond to specific interventions due to individual pharmacogenetic profiles will help shift the balance toward maximal benefit.

The alternative strategy to affect the risk-benefit balance is to lower the risk of the interventions, either by excluding individuals at risk for toxicity or through regional rather than systemic drug delivery or combination therapy. Lam et al. demonstrated minimal toxicity in a phase IIb lung chemoprevention trial of inhaled budesonide, a corticosteroid used for asthma, even though systemic treatment with steroids would be considered unacceptably toxic.¹⁷ Regional delivery to the oral cavity, lung, or colon (via delivery of agents that act locally and are not absorbed systemically) is particularly appealing. Similarly, agent combinations using lower doses than required for single agent treatment have the potential to increase efficacy while decreasing toxicity, although additive or unexpected toxicities from the combination require careful study. Meyskens and colleagues showed that the combination of a low dose of the nonsteroidal anti-inflammatory drug (NSAID) sulindac with the polyamine inhibitor difluoromethylornithine (DFMO) resulted in a superior clinical outcome and apparently less toxicity than would be expected from the use of NSAIDs alone.¹⁸ This trial showed an impressive 70% reduction in total adenoma burden and a greater than 90% reduction in advanced or multiple adenomas, the highest efficacy reported to date. Finally, alternative drug delivery schedules, such as periodic pulsatile treatment, may lower drug-associated toxicities, although this has not yet been adequately studied in animals or humans. Lubet et al. recently described excellent efficacy from intermittent delivery of gefitinib in a carcinogen-induced rat mammary cancer model system, suggesting that intermittent delivery, with its attendant decreased toxicity and thus increased tolerability, should be considered for future clinical trials.¹⁹

Phase II Clinical Trials

A number of different prevention phase II clinical trial designs exist due to the heterogeneity of the disease processes and the inherent difficulties in sampling tissues from different target organs. The challenges to designing phase II trials that are truly informative regarding the prevention of cancer are multiple. Identification of the appropriately high risk cohorts is difficult with our current limited understanding of cancer risk across multiple target organs. Furthermore, since prevention trials are performed before the development of a measurable cancer, it is difficult to measure the effect of an intervention on the process of carcinogenesis and to identify endpoints that are truly predictive of a cancer preventive effect. As a result, phase II cancer prevention trial design is a work in evolution. Some of the more common designs and relevant considerations have been summarized by the AACR Cancer Prevention Task Force.²⁰

Cohort selection

Optimizing the risk-benefit ratio requires the identification of high-risk cohorts who stand to gain the most from interventions. However, current risk assessment tools are very imprecise for most cancer types. For instance, even though the link between tobacco exposure and lung

cancer is among the strongest in all of cancer biology, only a minority of smokers develop lung cancer during their lifetime. Peto et al. estimated that the cumulative risk of lung cancer at age 75 to be 15.9% for men and 9.5% for women.²¹ Even identifying the smokers who are most likely to develop cancer has proven to be quite challenging.

To date, the most useful model predicting cancer risk has been the Gail model for breast cancer risk assessment, which was successfully used to identify candidates for the NSABP-P1 study of tamoxifen.²² Similar attempts were made by Bach et al. to develop a risk assessment tool to identify lung cancer risk in current and former smokers, based on the information available from the CARET beta-carotene lung cancer prevention trial of over 18,000 participants.^{23,24} While this tool is useful for individuals who fit the enrollment criteria for CARET, it is not applicable to individuals with different characteristics (for example, those younger than 50 years or with less smoking exposure). Spitz et al. have further expanded on lung cancer risk assessment to incorporate multiple exposures and family history as well as to assess risk in never smokers.²⁵ However, all of these models rely primarily on demographic information rather than on the specific molecular characteristics of a given individual and consequently have substantial limitations. Nevertheless, it should be noted, that attempts to improve on the Gail model for breast cancer risk assessment by adding information on common genetic variants led to very minimal prognostic improvement.²⁶ It therefore seems likely that identification of the actual somatic molecular changes occurring during carcinogenesis in a particular individual may be needed to improve the performance of risk assessment models.

The power of molecular prognostication is exemplified by the case of oral leukoplakia, which is a precursor to oral cancer with a very heterogeneous progression rate to cancer. While the rate of progression of dysplastic oral leukoplakia to cancer is typically described as 36% over 8 years, genetic damage in the form of loss of heterozygosity (LOH) at one or more specific chromosomal loci can identify subgroups of individuals with rates as high as 25–50% over 5 years.^{27,28} The risk-benefit balance and, consequently, the acceptable toxicity of interventions differ substantially in such high risk individuals compared with those individuals with lower risk molecular phenotypes. This information is being used as the basis for a phase III trial testing erlotinib in subjects with high risk oral leukoplakia, the Erlotinib Prevention of Oral Cancer (EPOC) trial.²⁹ Given the extraordinarily high risk of the cohort, this trial is the first oral leukoplakia trial that is able to be designed to have a definitive cancer incidence endpoint rather than relying on the effect of the intervention on the cancer precursor, namely oral leukoplakia. The development of improved risk assessment tools to identify the truly high-risk individuals who stand to gain the most benefit from preventive interventions remains a priority for cancer prevention research.

Intermediate Endpoints

Identification of appropriate (and informative) study endpoints is a critical aspect of any drug development program. Phase III cancer prevention trials are the “gold standard” in demonstrating preventive efficacy by assessing cancer incidence. Phase II preliminary efficacy cancer prevention trials, on the other hand, rely on short term, or intermediate, endpoints that are theoretically predictive of patient outcomes such as cancer incidence. In contrast to phase II cancer treatment trials which rely on tumor measurements to assess agent efficacy, phase II cancer prevention trials do not have easily measured primary trial endpoints for indicating preventive efficacy. Instead, early-phase cancer prevention trials generally assess surrogate efficacy measures such as histologic preneoplasia or proliferative indices that are even more distantly related to the definitive endpoint of cancer incidence than tumor shrinkage is related to survival.

To be useful, an intermediate marker should satisfy several criteria.^{30–32} The marker should be integrally involved in the process of carcinogenesis and its expression should correlate with

the disease course. The expression of the marker should differ between normal and at-risk epithelium, and it should be easily and reproducibly measurable in specimens likely to be obtained in clinical trials. Last, the expression of the marker should be modulated by effective interventions, and there should be minimal spontaneous fluctuations and no modulation by ineffective agents. A marker that satisfies these criteria then needs to be validated in prospective clinical trials.³²

No intermediate endpoint marker has passed these required rigorous validation measurements thus far. However, it is becoming clear that the complex molecular mechanisms that regulate tumor development involve a number of molecules and regulatory pathways controlling various cellular processes, including proliferation, differentiation, apoptosis, invasion through the basement membrane, and angiogenesis.³³ Classes of molecules found to be altered in epithelial cancers and preneoplastic lesions include oncogenes, tumor suppressor genes, growth factors or their receptors and molecules regulating cellular immortality, immune defense and tumor-associated angiogenesis. These aberrantly expressed molecules provide an opportunity to develop biomarkers for risk assessment as well as for monitoring response to chemopreventive or therapeutic interventions. For instance, it was recently reported that the PI3K pathway is upregulated early during lung carcinogenesis and that an intervention with the drug myo-inositol that resulted in regression of bronchial dysplasia also inhibited PI3K activation in the bronchial epithelium.³⁴ These data suggest that upregulated PI3K signaling could potentially identify smokers at increased risk for lung cancer and that pathway inhibition could serve as an endpoint for assessing treatment effect – a hypothesis that clearly requires further testing.

Nevertheless, even in the absence of validation, intermediate endpoints can significantly inform early phase drug development by demonstrating that the interventions affect the target epithelium. The most commonly used intermediate endpoints in phase II cancer prevention are histologic precursors to invasive cancer, generally referred to as “intraepithelial neoplasia.”³⁵ The natural history of such lesions can vary significantly, depending on the target organ and the severity of the abnormality. For instance, in the lung, approximately 3.5% of low or moderate dysplasias progress to severe dysplasia, 37% of severe dysplasias remain or progress, and approximately 50% of carcinomas in situ progress to invasive carcinoma within a two to three year follow-up period.^{36,37} Since one cannot predict which dysplasias will persist or progress, this argues for a randomized placebo controlled trial design whereby the “spontaneous” reversion rate in the placebo arm can be used as a comparison to account for the effects of the biopsies and for true biologic reversion. A number of phase II trials have used this approach in a variety of target organs. Fabian and colleagues studied DFMO in women with breast cytologic atypia diagnosed via random periareolar fine needle aspiration.³⁸ Lam et al. studied the inhaled steroid budesonide in smokers with bronchial dysplasia diagnosed by autofluorescence bronchoscopy,¹⁷ and Heath et al. studied celecoxib in subjects with Barrett’s esophagus with dysplasia identified via endoscopy.³⁹ All three of these studies were negative, suggesting either that all three agents were truly negative or that only a highly effective agent could be identified with an intraepithelial neoplasia endpoint.

A variety of other biomarkers, such as the Ki-67 proliferation index, have also been used as primary study endpoints, although the direct correlation between such biomarkers and cancer incidence is even more remote than the relationship between intraepithelial neoplasia and cancer.³¹ Prevention trials generally assess proliferation in preneoplastic or histologically normal epithelium in high risk individuals, a setting where proliferation is elevated but to a far lesser degree than in overt malignancy. Fabian et al. showed that six months of treatment with letrozole in postmenopausal women at high risk for breast cancer who were taking stable doses of hormone replacement resulted in a striking 66% decrease in the Ki-67 proliferation index in breast epithelial cells, in the absence of a discernible effect on cytology.⁴⁰ Similarly, Kim

and colleagues demonstrated a statistically significant decrease in Ki-67 in the histologically normal bronchial epithelium in smokers treated with celecoxib.⁴¹ Thus, proliferation appears to be more sensitive to modulation than histology – unfortunately, in the absence of data linking changes in proliferation with the definitive endpoint of cancer incidence, it is difficult to know how predictive this endpoint truly is.

An alternative to using single markers such as Ki-67 is to examine a panel of markers or even a gene expression profile. The effect of 12 months of treatment with celecoxib on gene expression in the normal colonic mucosa in subjects with hereditary nonpolyposis colon cancer was studied recently.⁴² These investigators found changes in expression in >1400 genes, albeit with a magnitude of change of <2-fold in the majority. The main biologic processes that were found to be affected were immune response, cell signaling and adhesion, response to stress, transforming growth factor- signaling, and regulation of apoptosis. This approach is similar to that of Gustafson and colleagues described above, who examined the effect of myo-inositol on gene expression in the normal bronchial epithelium and were able to show that inhibition of PI3K activation correlated with regression of dysplasia.³⁴ The use of gene expression analysis to study a small number of subjects treated with an intervention offers a faster and more efficient way to evaluate mechanisms of action of the intervention and to provide evidence of efficacy. Such an approach may eventually replace the relatively large phase IIb trials that study 100 or more participants with interventions lasting 3–6 months or more.

Early Phase Clinical Trial Designs

The design of clinical prevention trials has to account for different target organ biology and tissue accessibility, leading to a variety of trial designs currently in use for phase II trials. Depending on the nature of the endpoint being assessed, trials range from multi-month treatments with the aim of regressing intraepithelial neoplasia to short-term treatments with the aim of demonstrating an effect on a pharmacodynamic endpoint.²⁰ Several potential phase II trial designs are summarized in table 1. Longer treatment is thought to be necessary to reverse premalignant lesions, whereas pharmacodynamic endpoints or processes such as proliferation and a wide variety of alterations in gene or protein expression can be modulated within a few days to weeks. The amount of information learned differs substantially between the different designs.

As cancer treatment strategies become more targeted and less toxic and as our understanding of the biology of preneoplasia matures to reveal relevant molecular targets for early intervention, the same agents may become appropriate for both prevention and treatment. This provides unprecedented opportunities to assess chemopreventive efficacy during the use of agents for cancer treatment or in the presurgical setting. ‘Prevention-relevant endpoints’, such as biomarkers of proliferation or pharmacodynamic effects, can be assessed in short term presurgical settings or longer-term neoadjuvant settings while the patient is awaiting definitive surgical treatment. This has already been particularly well modeled using endocrine therapies in the setting of breast cancer.⁴³ Since acquisition of tissue occurs within the context of ‘standard of care’ and presumably large amounts of tissue (at least tumor tissue) become available at the time of definitive resection, these approaches have clear benefits. The negative of a pre-surgical or neo-adjuvant approach is that treatment duration is limited and thus may be too brief to demonstrate effects on intraepithelial neoplasia. In addition, it is the effect on intraepithelial neoplasia that is of most interest for assessing preventive agents, yet the amount of premalignant tissue at the time of resection is still likely to be quite limited.

Similar to the pre-surgical approach, assessment of ‘prevention-relevant’ endpoints can also be nested in cancer treatment trials which use agents that have potential for cancer prevention. If agents have an appropriately benign toxicity profile, this allows simultaneous early development for prevention and treatment indications. For example, bronchoscopies or

colonoscopies to assess agent effects on bronchial dysplasia and aberrant crypt foci, respectively, can be performed pre-treatment and at defined times during treatment in patients with an excellent performance status who are participating in phase II cancer treatment trials, since these premalignant lesions occur with high frequency in these patient populations. The obvious limitation of this trial design is the high progressive disease rate for advanced cancer populations, which may prevent the post-treatment evaluation. The need for additional invasive procedures such as bronchoscopies and colonoscopies is another difficulty of this approach. Nesting of 'prevention-relevant' endpoints into adjuvant therapy trials increases the likelihood of being able to perform the post-treatment assessment after appropriately long treatment duration, although these trials are fewer in number and currently are much more likely to include cytotoxic chemotherapy as part of the treatment regimen. However, simultaneous assessment of 'prevention-relevant' endpoints would considerably speed up new prevention agent development by giving an early indication of effectiveness, which may or may not need to be followed by dose titration to establish the optimal dose for true prevention indications.

Conclusions

The recent explosion of knowledge regarding the development of cancer offers hope for and challenges to the development of strategies to prevent cancer. As cancers arising at a variety of target organs are shown to be considerably more complex and molecularly heterogeneous than originally thought, prevention has also proven to be more complicated and elusive than initially anticipated. Rational selection of targets for intervention requires a greater understanding of the biology of the carcinogenic process. Since carcinogenesis occurs over time, potentially with different mechanisms assuming primary importance during different stages of cancer development, it is particularly important to understand the temporal progression of molecular abnormalities. Equally important is the identification of the appropriate high risk cohort that should be targeted for intervention. The proper risk-benefit balance can only be reached when the cohort's cancer risk is high enough to justify the potential toxicities from the intervention. Finally, there is a tremendous need to develop new models of clinical trials that can efficiently identify promising agents for cancer prevention. This requires identification of biomarkers that reflect clinical benefit, and, eventually, validation of these markers if they are to be used as surrogates. Novel technologies, including imaging modalities as well as molecular analyses of tissues and body fluids, will be needed to reach these goals.

References

1. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;190:1371–88. [PubMed: 9747868]
2. Vogel VG, Constantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes. *JAMA* 2006;295:2727–41. [PubMed: 16754727]
3. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Eng J Med* 2007;356:1928–43.
4. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet* 2009;374:301–14. [PubMed: 19586656]
5. Steinbach G, Lynch PM, Phillips RK, et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946–52. [PubMed: 10874062]
6. The ATBC Study Group. The Effect of Vitamin E and Beta Carotene on the Incidence of Lung Cancer and Other Cancers in Male Smokers. The Alpha-Tocopherol Beta Carotene Cancer Prevention Study Group. *N Eng J Med* 1994;330:1029–35.

7. Szabo E. Selecting Targets for Cancer Prevention: Where Do We Go from Here? *Nature Rev Cancer* 2006;6:867–74. [PubMed: 17036038]
8. Peppercorn J, Perou CM, Carey LA. Molecular subtypes in breast cancer evaluation and management: Divide and conquer. *Cancer Investigation* 2008;26:1–10. [PubMed: 18181038]
9. Ding L, Getz G, Wheeler DA, et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature* 2008;455:1069–75. [PubMed: 18948947]
10. Cohen MH, Johnson JR, Pazdur R. U.S. Food and Drug Administration drug approval summary: Conversion of imatinib mesylate (STI571; Gleevec) tablets from accelerated approval to full approval. *Clin Cancer Res* 2005;11:12–9. [PubMed: 15671523]
11. Blanke CD, Corless CL. State-of-the art therapy for gastrointestinal stromal tumors. *Cancer Invest* 2005;23:274–80. [PubMed: 15945512]
12. Dy GK, Miller AA, Mandrekar SJ, et al. A phase II trial of imatinib (STI571) in patients with c-kit expressing relapsed small-cell lung cancer: a CALGB and NCCTG study. *Ann Oncol* 2005;16:1811–6. [PubMed: 16087693]
13. Burger H, den Bakker MA, Stoter G, et al. Lack of c-*kit* exon 11 activating mutations in c-KIT/CD117-positive SCLC tumour specimens. *Eur J Cancer* 2003;39:793–9. [PubMed: 12651205]
14. Lam S, MacAulay C, le Riche JC, et al. A randomized phase IIb trial of anethole dithiolethione in smokers with bronchial dysplasia. *J Natl Cancer Inst* 2002;94:1001–9. [PubMed: 12096085]
15. Baron J, Sandler RS, Bresalier RS, et al. A Randomized trial of rofecoxib for the chemoprevention of colorectal cancer. *Gastroenterology* 2006;131:1674–82. [PubMed: 17087947]
16. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Eng J Med* 2005;352:1092–1102.
17. Lam S, le Riche JC, McWilliams A, et al. A randomized phase IIb trial of Pulmicort turbuhaler (budesonide) in persons with dysplasia of the bronchial epithelium. *Clin Cancer Res* 2004;10:6502–11. [PubMed: 15475437]
18. Meyskens FL Jr, McLaren CE, Pelot D, et al. Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial. *Cancer Prev Res* 2008;1:32–8.
19. Lubet RA, Szabo E, Christov K, et al. Effects of gefitinib (Iressa) on mammary cancers: preventive studies with varied dosages, combinations with vorozole or targetetin, and biomarker changes. *Mol Cancer Ther* 2008;7:972–9. [PubMed: 18375820]
20. Kelloff GJ, Lippman SM, Dannenberg AJ, et al. Progress in Chemoprevention Drug Development: The Promise of Molecular Biomarkers for Prevention of Intraepithelial Neoplasia (IEN) and Cancer (AACR Cancer Prevention Task Force). *Clin Cancer Res* 2006;12:3661–3697. [PubMed: 16778094]
21. Peto R, Darby S, Deo H, et al. Smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *Br Med J* 2000;321:323–9. [PubMed: 10926586]
22. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 1989;81:1879–86. [PubMed: 2593165]
23. Bach PB, Kattan MW, Thornquist MD, et al. Variations in lung cancer risk among smokers. *J Natl Cancer Inst* 2003;95:470–478. [PubMed: 12644540]
24. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Eng J Med* 1996;334:1150–55.
25. Spitz MR, Hong WK, Amos CI, et al. A risk model for prediction of lung cancer. *J Natl Cancer Inst* 2007;99:715–26. [PubMed: 17470739]
26. Wacholder S, Hartge P, Prentice R, et al. Performance of common genetic variants in breast-cancer risk models. *N Eng J Med* 2010;362:986–93.
27. Silverman S Jr, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. *Cancer* 1984;53:563–8. [PubMed: 6537892]
28. Rosin MP, Cheng X, Poh C, et al. Use of allelic loss to predict malignant risk for low grade epithelial dysplasia. *Clin Cancer Res* 2000;6:357–62. [PubMed: 10690511]
29. William WN, Heymach JV, Kim ES, et al. Molecular targets for cancer prevention. *Nature Rev Drug Discov* 2009;8:213–25. [PubMed: 19247304]

30. Lippman SM, Lee JS, Lotan R, et al. Biomarkers as intermediate end points in chemoprevention trials. *J Natl Cancer Inst* 1990;82:555–60. [PubMed: 2179569]
31. Szabo E. Assessing Efficacy in Early-Phase Cancer Prevention Trials: The Case of the Ki-67 Proliferation Index in Lung Cancer Prevention. *Cancer Prev Res* 2010;3:128–131.
32. Schatzkin A, Gail M. The promise and peril of surrogate end points in cancer research. *Nature Rev Cancer* 2002;2:1–9.
33. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;100:57–70. [PubMed: 10647931]
34. Gustafson AM, Soldi R, Anderlind C, et al. Airway PI3K pathway activation is an early and reversible event in lung cancer development. *Science Trans Med* 2010;2:26ra25.
35. O'Shaughnessy JA, Kelloff GJ, Gordon GB, et al. Treatment and Prevention of Intraepithelial Neoplasia: An Important Target for Accelerated New Agent Development. *Clin Cancer Res* 2002;8:314–46. [PubMed: 11839647]
36. Venmans BJW, van Boxem TJM, Smit EF, et al. Outcome of bronchial carcinoma in situ. *Chest* 2000;117:1572–76. [PubMed: 10858385]
37. Bota S, Auliac J-B, Paris C, et al. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence bronchoscopy. *Am J Respir Crit Care Med* 2001;164:1688–93. [PubMed: 11719311]
38. Fabian CJ, Kimler BF, Brady DA, et al. A phase II breast cancer chemoprevention trial of oral - difluoromethylornithine: breast tissue, imaging, and serum and urine biomarkers. *Clin Cancer Res* 2002;8:3105–17. [PubMed: 12374678]
39. Heath EI, Canto MI, Piantadosi S, et al. Secondary chemoprevention of Barrett's esophagus with celecoxib: results of a randomized trial. *J Natl Cancer Inst* 2007;99:545–57. [PubMed: 17405999]
40. Fabian CJ, Kimler BF, Zalles CM, et al. Reduction in proliferation with six months of letrozole in women on hormone replacement therapy. *Breast Cancer Res Treat* 2007;106:75–84. [PubMed: 17221152]
41. Kim ES, Hong WK, Lee JJ, et al. Biologic activity of celecoxib in the bronchial epithelium of current and former smokers. *Cancer Prev Res* 2010;3:148–59.
42. Glebov O, Rodriguez LM, Lynch P, et al. Celecoxib treatment alters the gene expression profile of normal colonic mucosa. *Cancer Epidemiol Biomarkers Prev* 2006;15:1382–91. [PubMed: 16835340]
43. Dowsett M. Preoperative models to evaluate endocrine strategies for breast cancer. *Clin Cancer Res* 2003;9:502S–10S. [PubMed: 12538507]

Figure 1.
Timing of Clinical Trials During the Process of Carcinogenesis

Table 1

Early Phase Clinical Trial Designs

Trial Type	Cohort	Comments
Prevention trial with IEN endpoint	High-risk subjects with IEN	Pre-screening for IEN is necessary
Prevention trial with molecular endpoint(s)	High-risk subjects, No IEN needed	Less pre-screening necessary; Less informative
Advanced cancer trial with nested 'prevention endpoint'	Cancer patients, +/- IEN	Potentially high drop-out rate due to progressive disease; Agent must be appropriate for prevention; Additional ("non- standard of care") tissue acquisition required
Adjuvant trial with nested "prevention endpoint"	Curatively treated cancer patients, +/- IEN	Agent must be appropriate for prevention; Additional ("non- standard of care") tissue acquisition
Presurgical or neoadjuvant model	Cancer patients prior to definitive surgery	Limited duration of treatment, primarily biomarker modulation; Tissue acquisition as part of "standard of care"

IEN=Intraepithelial neoplasia