Cancer chemoprevention: a rapidly evolving field

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Cancer chemoprevention involves the chronic administration of a synthetic, natural or biological agent to reduce or delay the occurrence of malignancy. The potential value of this approach has been demonstrated with trials in breast, prostate and colon cancer. The paradigm for developing new chemopreventive agents has changed markedly in the last decade and now involves extensive preclinical mechanistic evaluation of agents before clinical trials are instituted and a focus on defining biomarkers of activity that can be used as early predictors of efficacy. This review will summarise the current status of the field of chemoprevention and highlight potential new developments.

Given the steady increase in global cancer incidence with its associated morbidity and mortality, together with the spiralling healthcare costs of treatment, there is increasing interest in strategies for disease prevention. One approach with enormous potential is chemoprevention, which is defined as the use of natural, synthetic or biological agents to reverse, suppress or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease (Sporn, 1976). Interest in this area of research has markedly increased with improved understanding of the biology of carcinogenesis and the identification of potential molecular targets to perturb this process. Interest has been further stimulated by successes in the chemoprevention of breast, prostate and colon cancer, and the fact that there are now 10 FDA-approved (Wu et al., 2011a) agents for the treatment of precancerous lesions or cancer risk reduction.

Over the past 10 years, it has become apparent that the definition of chemoprevention should incorporate the concept of 'delay', which implies that the preventive effect may last for a finite period. The rate of tumour development is decreased even if the incidence eventually returns to that of the untreated population (Lippman and Hong, 2002), and many years or decades may be added to human lifespan.

Chemoprevention may involve perturbation of a variety of steps in tumour initiation, promotion and progression. Numerous potential mechanisms have been described and attempts have been made to broadly classify agents according to the effects they have on different stages of carcinogenesis (De Flora and Ferguson, 2005; Table 1). However, it is likely that many agents, particularly those that are dietary derived and multi-targeted, will have effects throughout the carcinogenic process. Compounds that inhibit cancer initiation are traditionally termed 'blocking agents'. They may act by preventing the interaction between chemical carcinogens or endogenous free radicals and DNA, thereby reducing the level of damage and resulting mutations which contribute not only to cancer initiation but also progressive genomic instability and overall neoplastic transformation. Protection may be achieved as a consequence of decreased cellular uptake and metabolic activation of pro-carcinogens and/or enhanced detoxification of reactive electrophiles and free radical scavenging, as well as induction of repair pathways (Yu and Kong, 2007; Valko et al., 2007).

Downregulation of chronic inflammatory responses and the production of reactive oxygen and nitrogen species may also contribute to the prevention of cancer initiation. Other protective processes include modulation of DNA methyl transferases to prevent or reverse the hypermethylation-induced inactivation of tumour suppressor genes. Inhibition of histone deacetylases has also been described among a variety of effects of blocking agents on epigenetic mechanisms of carcinogenesis (Hauser and Jung, 2008). Once initiation has occurred, chemopreventive agents may influence the promotion and progression of initiated cells; such compounds are often termed 'suppressing agents'. The major reported mechanisms contributing to this activity involve the inhibition of signal transduction pathways (for example, by targeting nuclear factor (NF)-κB) to perturb the effects of tumour promoters (Karin 2006), which would otherwise lead to cell proliferation. In some instances, hormones may promote tumour...
of individuals with premalignant lesions and administration of agents to prevent progression to invasive cancer. This would encompass the use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with colorectal adenomas. Definitions of primary and secondary chemoprevention vary and some groups now combine the two scenarios under the term primary chemoprevention. ‘Tertiary chemoprevention’ is defined as the administration of agents to prevent recurrence or second primary cancers in individuals who have undergone successful treatment of early disease.

There has been a major change in philosophy underlying the selection of promising chemopreventive agents in the last decade. Initially, selection was predominantly based on observational studies reporting an association between consumption of pharmaceutical (for example, aspirin) or dietary (for example, retinoids) components in a population, and a reduced incidence or mortality from cancer. Occasionally, early-phase clinical studies would be performed to explore duration of dosing and intermediate biomarkers of efficacy but in the majority of cases (for example, for beta-carotene) large randomised trials were undertaken, exploring the relative rates of cancer over many years in exposed and control populations without such prior information.

In recent years, there has been a more rigorous approach to the selection of agents for clinical development (Figure 2). Initial selection may still be based on epidemiological data suggesting an effect on cancer incidence, but subsequent extensive preclinical studies, using clinically achievable concentrations in models, which are relevant to human carcinogenesis, are increasingly undertaken before clinical trials begin (Scott et al, 2009). Preclinical testing should comprise a series of investigations, initially utilising in vitro and in vivo mechanistic assays. These can include measures of the effect of the agent under investigation on potentially important processes, such as inhibition of proliferation, modification of angiogenesis and inflammation or induction of apoptosis. Subsequently, in vivo testing may explore the prevention of tumour development as measured by incidence, overall burden or time to occurrence. Historically, animal models involved carcinogenic

**Table 1. Potential mechanisms of chemoprevention**

| Mechanisms of tumour-blocking agents | Mechanisms of tumour-suppressing agents |
|--------------------------------------|----------------------------------------|
| Scavenging of free radicals          | Alteration in gene expression          |
| Antioxidant activity                 | Inhibition of cell proliferation, clonal expansion |
| Induction of phase II drug-metabolising enzymes | Induction of terminal differentiation, senescence |
| Inhibition of phase I drug-metabolising enzymes | Induction of apoptosis in preneoplastic lesions |
| Induction of DNA repair              | Modulation of signal transduction      |
| Blockade of carcinogen uptake       |                                        |

**Table 2. Selected molecular targets of potential chemopreventive agents (effects may be tissue and cell specific as well as dose dependent)**

| Gene expression | Transcription factors | Protein kinases | Enzymes | Others |
|-----------------|-----------------------|----------------|---------|--------|
| Chemokines      | NF-κB                 | IkB kinase     | FTPase  | ICAM-1 |
| Cyclin D1       | AP-1                  | EGFR           | Xanthine oxidase | VCAM-1 |
| MMP9            | Egr-1                 | HER2           | Haemeoxygenase   | ELAM-1 |
| COX2            | STAT1                 | AKT            | uPA     | TF     |
| 5-LOX           | STAT3                 | JAK2           | GST     | Bcl-2  |
| iNOS            | STAT5                 | TYK2           | GSH-px  | Bcl-x  |
| IL-12           | PPAR-γ                | JNK            | P53     |
| TNF             | EpRE                  | PKC            |         |
| IL-6            | CBP                   | Src            | MDR     |
| IL-8            | β-catenin             | PKA            |         |
| Cyclin D1       |                       | Telomerase     |         |

**Potential value of chemoprevention**

The potential impact that chemoprevention could have on the death rate from cancer is evident from the way this approach has transformed the incidence of cardiovascular disease (Hansson, 2005). The introduction of drugs that suppress cholesterol synthesis, modify platelet aggregation or lower blood pressure has led to a steady fall in heart disease over the past 3 decades. The rate of cardiovascular disease was almost twice that of cancer for those under 85 years of age in the mid-1970s, but fell below that of cancer in 1999 (Figure 1; National Center for Health Statistics, Centers for Disease Control and Prevention, 2005). The cardiovascular community has been aggressive with chemoprevention, although many of the drugs they use can have serious or undesirable side effects. The major reason for successful uptake of preventive interventions has been the demonstration of measurable markers of increased risk of disease and death, such as hypertension and hypercholesterolaemia. It is clearly essential to identify similar measurable risk factors for cancer that will allow chemoprevention to be focused on subgroups of individuals, reducing anxieties about potential side effects and providing a surrogate end point of effective exposure (akin to the reduction in blood pressure), which may predict a reduced risk of disease.

**Agent selection for chemoprevention**

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exposure but, increasingly, transgenic/mutant rodent models (for example, ApcMin mice for colon cancer, TRAMP mice for prostate cancer) are now utilised, given their greater relevance to the complexities of human carcinogenesis (Abate-Shen et al, 2008). Such in vivo models can provide additional information on pharmacokinetics and safety. Target tissue levels can be measured to ensure appropriate delivery, and tissue concentrations producing an effect can be compared with subsequent human levels. This can provide a guide to appropriate dosing and scheduling (Wu et al, 2011a). Increasingly, preclinical testing may be linked to early-phase clinical trials. Potential biomarkers of activity may be developed in the laboratory and evaluated in patients with the hope that they can help determine optimal dose and be used in later
phase studies. Eventually, agents are selected for clinical development on the basis of these evaluations and the availability of an appropriate formulation (oral whenever possible) with minimal or no potential toxicity and low cost.

**TRIAL DESIGN**

Clinical chemoprevention agent development has utilised a similar model to new drug development in cancer therapy with sequential phase I, II and III studies (Lippman et al, 1994). Phase I studies have a primary aim of determining safety and pharmacokinetics such that a dose and schedule that is well tolerated by participants can be defined. Some phase I studies may incorporate preliminary assessments of potential biomarkers of effect (Lippman and Hong, 2002). Exposure is relatively short (usually up to 3 months). The choice of starting dose and schedule is extremely difficult and may be guided by preclinical studies. Dose conversions can be used, which aim to achieve plasma concentrations in humans, which should be safe and may approximate to levels producing a biological effect in preclinical models (Brown et al, 2010). PK data from phase I studies provide the actual levels that are achieved in humans, and these can be taken back into refined preclinical models to explore possible mechanisms of effect at clinically achievable concentrations. Studies may utilise existing drugs such as aspirin for which there is already extensive human data, and in this situation rapid progress to phase III trials can be contemplated.

Phase II trials, utilising the optimal dose previously defined, may follow with the primary aim of exploring, in relatively few patients, the impact of exposure on a biological end point. When potential biomarkers of effect are available, these can be examined in these patients. These trials may incorporate a placebo (phase IIb) to better define subtle side effects and tolerability, and also to more accurately measure biological effects.

Phase III trials usually involve thousands of participants over a long duration. Typically, there is randomisation between the agent under investigation and a placebo. Modification of a clinically relevant value, which is usually the incidence of malignancy, is the standard end point. Such trials may take many years and have huge costs.

Given the length of development of agents for chemoprevention, recent interest has focussed on phase 0 trials. These employ very low doses of experimental agent and utilise new methodologies and technologies to study pharmacokinetics at a dose that minimises any risk of toxicity (Kummar and Doroshow, 2011). It is hoped that this approach will provide information to help determine a rational dosage regime for future studies and will also lead to early termination of the development of agents that have unfavourable bioavailability, metabolism or distribution.

**BIOMARKERS**

The long latency of progression from premalignant lesions to invasive cancer offers the prospect of intervention to prevent disease. It is also a major obstacle for chemoprevention trials using cancer incidence as the primary end point, as it may take decades to obtain significantly different disease rates for an active agent. This puts a huge burden on trial participants, research infrastructure and financial budgets. An essential component to chemopreventive agent development, highlighted by consensus groups in the United States (Crowell, 2005) and Europe (Gerhauer et al, 2006), is a need to identify end points, which occur earlier than cancer, that accurately predict the potential to reduce cancer incidence. Targeting of these end points would aid choice of doses and schedules, and provide an early readout of potential efficacy. Few such easily measurable surrogates have been determined in carcinogenesis. Many approaches to biomarker selection have been taken and include the detection of high-risk adenomas or aberrant crypts in the colon and rectum, mammographic density in the breast, and changes of intraepithelial neoplasia in the head and neck and bladder. The Early Detection Research Network of the National Cancer Institute (United States) has a national programme to identify biomarkers associated with carcinogenesis utilising proteomic assessment of blood and urine (National Cancer Institute, 2008). An alternative, complementary approach that may be particularly useful in the early short-term trials would be to define mechanism-based pharmacodynamic biomarkers that reflect agent activity and correlate with efficacy in preclinical models, and determine their utility in humans.

**CLINICAL TRIALS OF CHEMOPREVENTION**

Several large randomised clinical chemoprevention trials have been undertaken – predominantly since the 1980s. There have been important positive results in breast and prostate cancer and familial adenomatous polyposis (FAP) but also several negative trials and four (in lung and colon cancer), which have suggested a harmful effect for the agents under investigation. Many lessons have been learnt from these experiences in trial design, and selection of agents and doses for future trials.

**Important positive trials.** The first trials to show a significant benefit for chemoprevention were undertaken in breast cancer. The Breast Cancer Prevention Trial (BCPT) included >13 000 women at increased risk of breast cancer (Fisher et al, 1998) and demonstrated a 49% reduction in invasive breast cancer and a 50% decrease in non-invasive disease, with the use of tamoxifen for 5 years compared with placebo. There was, however, a doubling of the risk of endometrial carcinoma and an increased incidence of thromboembolic events. Two other trials have been undertaken – International Breast Cancer Intervention Study (IBIS)-1) that compared tamoxifen against placebo and IBIS-2 that compared tamoxifen vs anastrozole. IBIS-1 (Cuzick et al, 2007) confirmed the protective effect seen in the BCPT but, importantly, has demonstrated that the increased risk of toxicity declined and was equivalent to that of patients on placebo by 10 years (or 5 years after tamoxifen discontinuation). Given concerns about the toxicity of tamoxifen and the effect it had in reducing women’s acceptance of its use as a chemopreventive, the Study of Tamoxifen And Raloxifene (STAR) study was initiated to compare these two agents for their effect on prevention and associated toxicities. Encouragingly, raloxifene was as effective as tamoxifen in reducing invasive breast cancer but did not increase the risk of endometrial tumours (Vogel et al, 2006). An update of the STAR trial (Vogel et al, 2010; increased median follow-up from 47 to 81 months) showed that raloxifene became less effective than tamoxifen in reducing invasive cancer but retained its greater safety profile. Both tamoxifen and raloxifene have obtained FDA approval for breast cancer prevention. The aromatase inhibitor, exemestane, has also been shown to have a chemopreventive effect for women with at least one risk factor for disease. A recent analysis showed a 65% relative reduction in the annual incidence of invasive disease (Goss et al, 2011).

Two positive large trials have explored the chemoprevention of prostate cancer, with cancer incidence as the end point. The Prostate Cancer Prevention Trial compared the 5α-reductase inhibitor, finasteride, with placebo given for 7 years in 18 882 men. At the time of analysis, 86.3% of participants had completed 7 years of treatment. There was a 26% reduction in the diagnosis of prostate cancer in the finasteride arm (P<0.001), but the protective effect appeared to be limited to lower grade tumours.
Cancer chemoprevention (Thompson et al., 2003). There was an increase in the number of biopsy cases with higher grade disease (1.8% vs 1.1%), which raised concerns. Subsequent analysis of prostatectomy specimens suggested that this observation was an artefact resulting from the effect of finasteride on prostate size, which affected the sampling in biopsy specimens rather than being a true increase (Lucia et al., 2007). Unfortunately, partly because of the initial findings, the FDA has not approved finasteride for prostate cancer chemoprevention. A subsequent randomised trial, the Reduction by Dutasteride of Prostate Cancer Events, demonstrated that dutasteride (another 5α-reductase inhibitor) reduced the risk of biopsy proven prostate cancer by 23% compared with placebo but, as with finasteride, the major benefit was in the prevention of lower grade malignancies (Andrieu et al., 2010).

Preclinical and epidemiological studies have shown huge promise for the role of NSAIDs to reduce colorectal cancer risk. Despite this potential, no prospective trials to date have studied the impact on colorectal cancer as a primary end point. Prospective randomised controlled trials with cardiovascular disease as the primary end point have shown, from secondary analyses, reductions in the development of colorectal cancer and death from malignancy. The first publication of long-term follow-up of participants in five trials showed that daily aspirin at any dose reduced the risk of colorectal cancer by 24% and of associated mortality by 35% after a delay of 8–10 years (Flossman and Rothwell, 2007). Subsequently, analysis (Rothwell et al., 2010) using data from eight randomised trials found that daily aspirin use at any dose was associated with a 21% reduction in all cancer deaths, with the benefit only apparent after 5 years. This work was extended to include an additional 43 randomised trials of daily aspirin. Cancer death was reduced by 15%, with benefits seen within 3 years at high doses (≥300 mg per day) and after 5 years for lower doses (<300 mg per day). These data suggest that low-dose aspirin may reduce the risk of sporadic colorectal adenomas within a few years but requires 5 years to produce an effect on invasive cancer and cancer death (Rothwell et al., 2012). At high doses, however, it appears that aspirin may reduce cancer death with a direct effect on the growth and spread of established tumours as well as their initiation, as cancer death was reduced within 2–3 years following randomisation. Further analysis of five trials showed that aspirin reduced the risk of cancer with distant metastasis, particularly for adenocarcinomas (Algra and Rothwell, 2012). Some patients were included with localised indolent malignancy, and for those who were assigned aspirin there was a lower risk of developing metastases during subsequent follow-up.

Questions still remain, however, as to whether aspirin should be routinely recommended for cancer prevention. The main concerns are that two large prospective trials, the Women’s Health and Physicians’ Health Studies (Steering Committee of the Physicians’ Health Study Group, 1989; Harris et al., 2003), were negative and the cardiovascular trials occurred before cancer screening and surveillance were routine. Nevertheless, the recent data does suggest that aspirin can reduce cancer incidence and death, and this effect is delayed. Hopefully, a clearer guide to the ratio of benefit to risk will emerge with completion of two ongoing US trials.

For those individuals with hereditary colon cancer (Lynch syndrome), a randomised study has shown a significant benefit for aspirin and has led to a second prospective study, which aims to define optimal dosing (Burn et al., 2011).

Selective COX2 inhibitors were introduced into clinical trials as an alternative to standard NSAIDs, given their reduced propensity to induce gastrointestinal toxicity. The initial study in 83 patients with FAP demonstrated a 28% reduction in adenoma burden (Steinbach et al., 2000). These results led to the accelerated approval of celecoxib for the treatment of FAP. Two subsequent trials of celecoxib confirmed the preventative effect against recurrent adenomas but both studies were associated with two- to three-fold increases in serious cardiovascular events (Solomon et al., 2005). A recent study with the fish oil extract, eicosapentaenoic acid in patients with FAP demonstrated a similar reduction in adenoma burden to that seen with celecoxib but with minimal toxicity (West et al., 2010), and this is being further developed.

Important negative trials. Two of the earliest chemoprevention trials were based on data linking cancer risk reduction and intake of carotenoids. These included smokers, with lung cancer incidence as the end point. The α-tocopherol (vitamin E), β-carotene (ATBC) prevention study enrolled 29 133 men with a randomisation to α-tocopherol, β-carotene, a combination of both or a placebo. The first results were alarming, showing a 18% increased incidence of lung cancers, increased cardiovascular disease and an 8% increased overall mortality for those on β-carotene (The Alpha-Tocopherol, Beta–Carotene Cancer Prevention Study Group, 1994). Subsequent analysis revealed the adverse effect to be stronger in men with a modest alcohol intake and smokers of >20 cigarettes daily (Albanes et al., 1996). Interestingly, prostate cancer incidence and death were reduced in the vitamin E arms (by 32% and 41%, respectively). The β-Carotene And Retinol Efficacy Trial included men with occupational asbestos exposure or men and women who were current or former cigarette smokers (18 314 participants) randomised to β-carotene plus retinyl palmitate or placebo. This was closed early because those in the intervention arm had higher lung cancer death rates (17% and 28%, respectively) and higher rates of cardiovascular disease mortality (Omenn et al., 1996). Further investigation of β-carotene for cancer prevention was discontinued as a result.

One of the largest prevention studies was the Selenium and vitamin E Cancer Prevention Trial (Lippman et al., 2009). Men (35 534) were randomised to receive α-tocopherol, selenium, both agents and a placebo. Unfortunately, the trial was closed early after an interim analysis indicated an extremely low likelihood of producing a positive result. A later report showed a significant 17% increase in the risk of prostate cancer among those who received vitamin E (Klein et al., 2011). Detailed analyses were subsequently undertaken on two smaller previous studies that had suggested a protective effect from selenium. In both of these, benefit of selenium was seen but was limited to those with lowest baseline blood selenium levels (Duffield-Lillico et al., 2002). The benefits and risks of nutritional supplementation may thus depend on prior exposure – those with marginal or deficient nutrient intakes may be the group to benefit whereas those whose intake is already adequate or high may experience harm.

An explanation for the detrimental effects seen in the prostate and lung prevention trials may thus be the dose of experimental agent chosen. Selenium and β-carotene are naturally occurring dietary constituents, which are important in normal human physiology. It is plausible that a U-shaped dose–response curve exists where either deficiency or supraphysiological doses may cause harm. The negative results from these large expensive trials have led many to re Assess the design of clinical chemoprevention studies and to move towards smaller studies focussing on higher-risk individuals, and to rely on more detailed prior preclinical mechanistic evaluation to provide information that may better guide dose selection.

CONCLUSIONS AND FUTURE DEVELOPMENTS

Chemoprevention is a relatively new field for research. In recent years, preclinical and clinical development strategies have evolved so that agents are increasingly selected for further development based on mechanisms of action rather than relying on historical epidemiological observations. Many new targets have been defined.
including the upregulation of Nrf2, NF-κB and various members of the STAT family of transcription factors. New agents that target the cyclin family of cell cycle regulators – cyclin D1, D2 and D3 – are being actively pursued, as these are often abnormally expressed in pre-neoplasia. The approach of Short-term Intermittent Therapy to Eliminate Premalignancy (SITEP) (Wu and Lippman, 2011b) is being investigated and is based on the hypothesis that intermittent therapy may eliminate premalignant cells through selective apoptosis induced by synthetic lethal interactions. It has resulted in efficacy in mouse models of carcinogenesis that result from APC and KRAS mutations, and is being tested in breast cancer chemoprevention, based on the synthetic lethality between the mutated tumour suppressor genes BRCA1 or BRCA 2, and PARP1 (Fong et al, 2009). Increasing interest is focusing on a move from single agent chemoprevention to combination approaches. An important trial combined difluoromethyllornithine and sulindac in 375 patients with a history of resected adenomas and demonstrated a 60% reduction in recurrence rates (Meyskens et al, 2008). As with chemotherapy, the hope is that such an approach will produce a synergistic or additive effect and will also allow their lowest active doses to be chosen to reduce toxicity.

Although there have been several major achievements in chemoprevention, there is clearly a huge amount to be done to mirror the successes seen in cardiovascular medicine. It is frustrating that one of the agents with great potential in colorectal cancer, aspirin, still has not been properly assessed in prospective randomised trials in this disease. Hopefully, important information will be obtained on its tolerability in large populations from the recently completed AspECT trial in Barrett’s oesophagus, and this will move the field forward. Much more work needs to be undertaken with nutritionally derived agents. It is estimated that $300 billions is spent on dietary supplements each year (Cohen, 2012) and yet no chemoprevention trials with these have yielded positive outcomes. An important lesson obtained from experience with selenium in prostate cancer prevention is the need to understand the role of these agents in populations with different endogenous exposure, leading to varying tissue levels before study entry.

One further development that is aimed at reducing the size, cost and duration of clinical trials, thereby enabling more agents to be examined, is the selection of higher-risk individuals for inclusion in studies. Many approaches have been taken to identify clinico-pathological variables and molecular markers that can predict which patients may have premalignancy. One current approach involves modelling germ line and somatic markers of risk and relapse in patients who may have premalignancy. One current approach involves modelling germ line and somatic markers of risk and relapse in patients who may have premalignancy. The goal is to understand the role of these agents in populations with different endogenous exposure, leading to varying tissue levels before study entry.

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