FEATURE

Pharmacologic prevention of cancer

Do we have sufficient evidence to support clinical practice?

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ABSTRACT

A number of medications used to treat common non-cancer conditions appear to have some activity in preventing or slowing cancer growth. This article focuses on commonly used drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), statins, metformin and bisphosphonates, and examines their possible mechanisms of action in preventing cancer development and progression. The authors review the evidence accumulated on each of these medications to date, discuss the balance of benefits and adverse effects, and present current clinical recommendations. The significant challenges of research into chemoprevention and novel strategies are described.

Keywords: Chemoprevention, cancer research, cancer epidemiology

Cancer is a leading contributor to disease burden and healthcare cost despite the fact that a substantial portion of cancer is preventable. Interest in cancer chemoprevention, defined as the use of natural, synthetic, or biologic agents in preventing the initiation and suppressing the progression and recurrence of cancer, has been growing. For a drug to be considered appropriate as a cancer prevention agent, overall benefit and risk must be considered: the drug has to be effective in improving one or more cancer outcomes (incidence, mortality, survival, recurrence) while posing very low risk of adverse effects. This article examines scientific evidence from recent studies on cancer chemoprevention of common drugs (nonsteroidal antiinflammatory drugs [NSAIDs], statins, metformin and bisphosphonates) in terms of their mechanism of action, impact on cancer outcomes and adverse effects, presents clinical recommendations, and describes research challenges and opportunities. Table 1 (page 17) and Table 2 (page 18) summarize evidence and clinical recommendations.

SCIENTIFIC EVIDENCE

Aspirin and other NSAIDs

In cardiovascular disease (CVD), the benefit of aspirin is well established in secondary prevention, though uncertainty around benefit in primary prevention persists. NSAIDs reduce the formation of prostanoids known as tissue-specific signaling lipids by suppressing cyclooxygenase (COX) activity. However, aspirin acts somewhat differently than other NSAIDs, as it permanently inhibits COX isozymes COX-1 and COX-2 via irreversible acetylation of the enzymatic active site. The inhibition by other NSAIDs is reversible. Exact mechanisms for the anticancer effects of aspirin and NSAIDs are not completely clear but direct inhibition of COX-2 plays a primary role. Other possible mechanisms include inhibition of several signaling pathways (NF-kB and mTOR), induction of polyamine catabolism, and activation of adenosine monophosphate-activated protein kinase (AMPK). These effects require a relatively high dose of NSAIDs. However, at doses as low as 30 mg/day, aspirin can inhibit COX-1 activity in platelets, which may trigger downstream signaling events leading to enhanced cellular apoptosis, and reduced proliferation and angiogenesis.

There is now strong evidence from both observational studies and randomized controlled trials (RCTs) that aspirin use reduces the risk of colorectal cancer (CRC) and other gastrointestinal (GI) cancers, including esophageal and gastric cancers. Daily aspirin use reduces CRC cancer incidence and mortality by more than 20% in RCTs. Alternate-day use does not produce significant benefit. Secondary analysis of RCTs also suggest that aspirin reduces mortality and metastasis of CRC and several other cancers. However, the absolute benefit is relatively small: aspirin use could prevent 34 deaths from CRC over 100,000 patient-years (e.g. 10,000 persons followed for 10 years) and the benefit only appears after at least 5 years of regular aspirin use. An increasing number of observational studies show that aspirin and NSAID use is associated with lower risk for prostate cancer and breast cancer. Epidemiologic research findings for other cancer types are more mixed. Aspirin use increases the risk of bleeding at various sites, notably GI bleeding and hemorrhagic stroke, by 30% to 60%. An estimated 68 to 117 such adverse events will occur in every 10,000 patients during a 10-year followup, though the risk of adverse events falls after around 3 years of use.
Statins
Statins are a class of cholesterol-lowering medications that reduce the risk of CVD in people at risk, and likely for those at lower risk as well. Statins block the mevalonate pathway of cholesterol synthesis by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme-A reductase. The inhibition of this enzyme prevents the formation of mevalonate and its downstream products, including cholesterol, retinoid and the isoprene moieties, which are involved in the cell cycle regulation and signal transduction involved in cancer development. There is evidence showing that low cholesterol levels are associated with decreased cancer incidence and aggressiveness. Potential cholesterol-independent mechanisms involve the inhibition of cellular proliferation (through the induction of G1/S arrest and/or G2/M arrest) and angiogenesis, and the induction of apoptosis of tumour cells. Anti-inflammatory effects may also play a role.

Meta-analyses of observational studies show that statin use might be associated with reduced incidence of ovarian cancer, hematologic cancer, liver cancer, CRC and prostate cancer, while not for other cancer types (kidney, skin, lung, breast and bladder). Statins have also been associated with lower overall cancer mortality in prostate, breast and CRC in observational studies. However, none of these associations has been validated in RCTs. Epidemiologic evidence is emerging to indicate that statin use may prevent recurrence and improve survival in certain cancer types. For instance, statin use appears to prevent recurrence of prostate cancer among patients who have received radiotherapy (but not among radical prostatectomy patients), and breast cancer, though these benefits have not been confirmed in RCTs.

Guidelines from the American College of Cardiology/American Heart Association recommend the use of statins in preventing CVD among patients at relatively high risk for CVD. Muscle pain is the most common adverse effect with statins, and other adverse effects include liver damage, increased blood sugar levels and the development of type 2 diabetes mellitus (T2DM), memory loss, and sleep problems. One RCT showed patients on statin treatment have similar rates of most adverse effects compared to a placebo group, but higher rates of newly-diagnosed T2DM. Serious concerns about the accuracy of these estimations and the consequences of inaccuracy have been raised. In the UK, guidelines now recommend that physicians assess a patient’s risk for T2DM prior to initiating statin treatment and monitor the risk during treatment.

Metformin
Metformin is an oral antihyperglycemic agent commonly used in the treatment and prevention of T2DM. Metformin decreases hyperglycemia by suppressing hepatic glucose production and GI tract glucose absorption and by increasing insulin sensitivity and peripheral glucose uptake. Hyperglycemia and secondary hyperinsulinemia may contribute to the relationship between T2DM and increased risk of several cancers, and metformin could act indirectly to reduce insulin-sensitive tumour growth and progression. Metformin directly impacts cancer cell mitochondrial respiration leading to activation of AMPK, which controls energy homeostasis in cells.

Epidemiologic studies suggest that T2DM is associated with increased risk for some cancers (especially CRC, liver, breast and pancreatic cancers) but with a reduced risk for prostate cancer. There is a growing body of evidence showing lower risk for prostate cancer incidence and possibly recurrence among diabetic metformin users. Diabetic patients treated with metformin are less likely to be diagnosed with breast cancer, CRC, pancreatic cancer and hepatocellular cancer, and to die from certain types of cancer (breast cancer and CRC) and any cancer. Methodologic limitations in these studies, including confounding by T2DM and other medical indications and time-related bias, are important to consider in interpreting these findings. Studies showing lower lung cancer risk among metformin users are particularly controversial due to confounding by smoking. A 2014 systematic review and meta-analysis found that metformin use was associated with reduced overall cancer incidence (18% reduction) and mortality (10% reduction) after controlling for body mass index and time-related bias, though no associations were found for specific cancer types. A number of earlier trials did not support the cancer preventive effects of metformin.

Ongoing trials, primarily in breast and prostate cancer, are expected to shed light on the issue. Little is known about the association between metformin use and cancer risk among nondiabetic patients.

Metformin is unlikely to cause hypoglycemia and is generally safe. GI irritation (e.g. diarrhea, cramps, nausea, vomiting and increased flatulence) is the most common adverse effect of metformin use. Metformin has been associated with serious lactic acidosis that is related to other comorbidities, such as impaired liver and renal functions. Other side effects, including weight loss and vitamin B12 deficiency, have also been reported among metformin users.

Bisphosphonates
Bisphosphonates are used to prevent and treat osteoporosis and to relieve pain from bone metastases in cancer patients. Bisphosphonates can directly target cancer cells or exert indirect anticancer effects by affecting the bone microenvironment and immune system. Bisphosphonates inhibit tumour cell adhesion, migration, invasion and proliferation, and induce tumour cell apoptosis when used as single agents or along with other drugs.

Observational studies and clinical trials have demonstrated improved survival in postmenopausal women with breast cancer after bisphosphonate use, likely due to their protective effect against bone metastasis and fracture. Observational studies have also indicated that bisphosphonates might improve survival in patients with lung cancer. Bisphosphonates have been associated with a lower incidence of CRC and breast cancer. However, two recent RCTs found that 3 to 4 years of bisphosphonate treatment did not decrease the risk of invasive postmenopausal breast cancer.
TABLE 1. Summary of evidence on human cancer prevention drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Proposed mechanism</th>
<th>Beneficial effect of cancer prevention</th>
<th>Examples of adverse effects</th>
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<tr>
<td></td>
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<td>Observational studies</td>
<td>Clinical trials</td>
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<tr>
<td>Aspirin and NSAIDs</td>
<td>COX-2 inhibition at high dose and COX-1 inhibition in platelets at low dose; COX-independent pathways (e.g. inhibition of NF-kB signaling pathway)</td>
<td>↓ incidence and mortality of CRC, esophageal, gastric, prostate, and breast cancers; ↓ CRC metastasis</td>
<td>↓ incidence and mortality of CRC when used daily, rather than at alternate days; ↓ CRC metastasis</td>
</tr>
<tr>
<td>Statins</td>
<td>Cholesterol level reduction; cholesterol-independent pathways (tumour cell proliferation inhibition, apoptosis induction, antiinflammatory effect)</td>
<td>↓ incidence of ovarian, hematologic, liver, colorectal, and prostate cancers; ↓ mortality of overall cancer, prostate, breast and colorectal cancers; ↓ recurrence of prostate and breast cancers</td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>Insulin level reduction and subsequent insulin-sensitive tumour growth and progression inhibition; energetic stress induction in tumour cells</td>
<td>↓ incidence of breast, CRC, pancreatic, prostate, and hepatocellular cancers and overall cancer; ↓ mortality of breast and colorectal cancers and overall cancer; ↓ recurrence of prostate cancer</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Direct impact on tumour cell proliferation and apoptosis; interference with bone micro-environment; stimulation of immune system</td>
<td>↓ breast and colorectal cancer incidence; ↑ breast and lung cancer survival</td>
<td>↑ breast cancer survival</td>
</tr>
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Bisphosphonates may cause mild adverse effects (GI irritation) in some patients, but severe adverse effects are rare. Use of bisphosphonates is associated with higher risk for osteonecrosis of the jaw in cancer patients, but other medications may contribute to the association as well. There is no evidence of detrimental effect on cardiovascular mortality, although an observed higher risk of atrial fibrillation remains a concern. Findings regarding other severe adverse effects, including esophageal cancer, severe suppression of bone turnover, and severe musculoskeletal pain, have been inconsistent.

CLINICAL RECOMMENDATIONS

As of 2011, the US Food and Drug Administration (FDA) had approved 10 agents, including 1 vaccine and 9 medications, for cancer chemoprevention. Medical professional organizations have made a few clinical recommendations on pharmacologic prevention of cancer, and there is continued debate around some of those recommendations. Despite strong evidence from observational studies and RCTs, use of aspirin and NSAIDs for the prevention of CRC or other cancer types is not recommended in clinical practice due to uncertainties about the balance of benefits and risks. The US Preventive Services Task Force (USPSTF) recommends against the routine use of aspirin and NSAIDs for the prevention of CRC in individuals at average risk for CRC. Other organizations, such as the American Cancer Society and the American Gastroenterological Association, offer no recommendations or do not recommend the use of aspirin and NSAIDs in CRC prevention. New evidence has emerged since the release of those recommendations, and it may be time to revisit the overall benefit-risk assessment of long-term use of low-dose aspirin in CRC prevention.

Regarding metformin, statins and bisphosphonates, it is obvious that evidence from RCTs is needed before physicians will really be able to discuss with patients their value in cancer prevention.

RESEARCH CHALLENGES AND OPPORTUNITIES

Most of the evidence showing reduced cancer risk in people taking common drugs for noncancer conditions comes from observational studies and has only rarely been validated in RCTs, the gold standard for determining an intervention’s efficacy. Despite their limitations, observational studies are critical in building the case for eventual RCTs, which are time-consuming, costly and suffer their own limitations, including a lack of external generalizability. Cancer incidence and outcome is often not the primary endpoint in RCTs, and most include a short followup and small number of cancer cases. Registry-based randomized trials, a novel trial design using existing high-quality population and clinical registries, is promising, as it follows randomization principals but is more efficient and less expensive. Mobile technologies hold promise for improving trial efficiency via remote recruiting and monitoring of patients. Other innovations in clinical trials such as adaptive design and Bayesian methods, could also improve cancer chemoprevention trials.

The use of electronic medical records (EMR) in clinical research has advanced quickly thanks to modern information...
technology and data mining methods. However, using EMR data is challenging, as much of the information is entered as unstructured text and images. Using natural language processing (NLP) methods, researchers have successfully extracted clinical notes in order to evaluate drug use history, disease progression, treatment toxicities and personal factors such as smoking. NLP could be used to examine the association between patient drug use and cancer survival (and even cancer diagnosis if the length of follow-up is sufficient) efficiently using existing clinical data.

The long induction and latency periods in cancer development, and consequent requirement for long-term follow-up, is a major obstacle to trials. Biomarkers may be used as surrogate endpoints if they can accurately and precisely predict the risk of cancer. Despite the challenges in biomarker selection and validation, biomarker-driven cancer chemoprevention still appears promising and will likely accelerate the discovery of new agents. A new concept called short-term intermittent therapy has been proposed as a way to prevent cancer by targeting genetic and epigenetic changes in premalignant cells; short-term intermittent dosing techniques would reduce adverse effects. Recently, a new trial design (basket trial) based on genetic biomarkers was developed to study targeted treatment of thoracic malignancies, and this design may have applications in future prevention trials. Molecular biomarkers such as drug-induced cytochrome P450 expression profiles and cytochrome P450 gene polymorphisms could be used to monitor early toxicities of prevention agents.

Developments in precision medicine will also impact the study of chemopreventive agents. A recent study found that regular use of aspirin and NSAIDs reduced the risk of CRC only in individuals with certain genotypes. In addition to genetic variation, differences in diet and lifestyle may also determine the preventive effects of medications. Oncology is the centrepiece of the newly unveiled precision medicine initiative in the US, and we can look forward to an expansion of research to help identify individuals who will benefit most from chemoprevention and to develop personalized pharmacologic interventions.

References

**TABLE 2. Clinical recommendations on pharmacological prevention of cancer**

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Recommendations</th>
<th>Organization</th>
<th>Year</th>
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<tr>
<td>Breast</td>
<td>Clinicians should offer tamoxifen or raloxifene to women at increased risk for breast cancer and at low risk for adverse reactions.</td>
<td>USPSTF</td>
<td>2013</td>
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<tr>
<td>Breast</td>
<td>Clinicians should discuss the option of chemoprevention with women at increased risk for breast cancer (i.e. tamoxifen for pre- or postmenopausal women aged ≥35 years and at increased risk, or with lobular carcinoma in situ (LCIS); raloxifene and exemestane for postmenopausal women aged ≥35 years or with LCIS).</td>
<td>ASCO</td>
<td>2013</td>
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<tr>
<td>Prostate</td>
<td>Clinicians are encouraged to discuss the benefits of 5-alpha reductase inhibitors (ARIs) for 7 years for the prevention of prostate cancer with asymptomatic men willing to undergo periodic monitoring and men who are taking 5-ARIs for benign conditions.</td>
<td>ASCO-AUA</td>
<td>2008</td>
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<tr>
<td>Colorectal</td>
<td>Routine use of aspirin and NSAIDs in individuals at average risk for colorectal cancer is not recommended.</td>
<td>USPSTF</td>
<td>2007</td>
</tr>
<tr>
<td>Lung</td>
<td>Aspirin, COX-2 inhibitors, and other chemopreventive agents are not recommended for individuals at increased risk of lung cancer or with a history of lung cancer.</td>
<td>ACCP</td>
<td>2007</td>
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