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DRUG REPURPOSING IN ONCOLOGY: EVIDENCE FOR METFORMIN, STATINS AND ASPIRIN

MAAIKE HOEKSTRA[1]*, MEGAN LINDQVIST[2], SOFIE CLAES[3]

Affiliation [1]Department of Neuropharmacology, Twente Institute of Pharmaceutical Technology, Hengelo, Netherlands
[2]Department of Neuropharmacology, Shenandoah Valley College of Pharmacy, Harrisonburg, USA
[3]Department of Pharmacology, Kempen Centre for Pharmaceutical Analysis, Geel, Belgium

*Corresponding author: Maaike Hoekstra, m.hoekstra@tipt.nl
ORCID iD: Maaike Hoekstra 0000-0001-1262-8733; Megan Lindqvist 0000-0001-2861-6112; Sofie Claes 0000-0001-4755-2206

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Abstract

Drug repurposing offers a faster and cheaper route to new cancer treatments than de novo development, and three long-established medicines, metformin, aspirin and the statins, have drawn the most attention. This narrative review summarises published mechanistic, observational and trial evidence for each agent in oncology, and it reports no new data. Aspirin has the most consistent support for colorectal cancer prevention, especially in people at hereditary risk, although results in older adults are less reassuring. Metformin and statins show encouraging associations in cohort studies, but randomised trials in established cancer have mostly been neutral. Time-related bias, dose and the lack of tumour selection remain the main gaps in the evidence.

1. INTRODUCTION

Bringing a new anticancer drug from the bench to the clinic takes well over a decade, costs a very large sum, and fails more often than it succeeds. Drug repurposing, also called repositioning, tries to shorten that path by looking for fresh uses of compounds whose pharmacokinetics, toxicity and manufacturing are already understood [1, 2]. The idea is old, and many early successes came by accident, but it has gained ground as large prescription databases, cheaper molecular profiling and better knowledge of tumour biology have made unexpected signals easier to find. Oncology suits the approach, because tumours depend on growth factor signalling, inflammation and altered metabolism, and all of these are also touched by medicines that were developed for something else entirely [1].

Metformin, aspirin and the statins were chosen for this review because each is taken daily by millions of people, each has decades

of safety experience, and each has generated a substantial body of cancer-related research. All three are inexpensive as generics, which matters in health systems that are struggling to pay for new oncology drugs. They also act on different parts of the biology that Hanahan and Weinberg described as enabling features of cancer, namely sustained proliferative signalling, tumour-promoting inflammation and deregulated cellular energetics [3]. This review brings together published mechanistic work, cohort studies and randomised trials for each drug. It reports no new data, and it tries to show where the signals are strong, where they are thin, and why they sometimes disagree.

Repurposing evidence usually accumulates in a recognisable order. A laboratory observation suggests a plausible mechanism, pharmacoepidemiology then looks for a signal among people already taking the drug, and only afterwards do randomised trials test whether the signal is causal [1]. The order matters because each stage has its own weaknesses. Cell-line work often uses concentrations that patients never reach, cohort studies are open to bias, and trials are expensive enough that they tend to be done in advanced disease, where an old drug has the hardest job. Prevention and treatment are also different questions. A medicine that lowers the chance of a tumour forming over years may do nothing for an established, genetically unstable cancer [2, 3].

2. METFORMIN

The first widely cited signal came from Scotland, where a record-linkage study of people with type 2 diabetes found that those who had been prescribed metformin were less likely to develop cancer than those given other glucose-lowering treatment [4]. Further cohort studies and meta-analyses over the next decade tended to point the same way. The result attracted attention partly because it fitted an attractive story, in which a drug that lowers circulating insulin might also starve insulin-responsive tumours. Methodologists were less impressed. Suissa and Azoulay showed that many of the early analyses contained time-related biases, particularly immortal time bias, which can make a drug look protective when it is not, and they argued that the more carefully designed studies showed far smaller effects [5].

At the cellular level the picture is more detailed than a single target. Metformin accumulates in mitochondria and inhibits complex I of the respiratory chain, which lowers ATP production and raises the AMP to ATP ratio [6, 7]. That change activates AMPK, a finding first shown in cultured cells and later confirmed in tissue [8], and the upstream kinase LKB1 appears to be needed for much of the response [9]. Active AMPK then phosphorylates TSC2, which switches off mTOR signalling and slows protein synthesis and cell growth [10]. Experiments with cancer cells show that complex I inhibition also limits tumour growth in some settings, particularly when cells depend on oxidative metabolism [7]. Not every effect needs AMPK, however, and the relative contribution of each route is still argued over [11].

A second, indirect route runs through the endocrine system. Metformin lowers fasting insulin and, to a smaller extent, circulating glucose, and because the insulin and insulin-like growth factor receptors can drive proliferation and survival in epithelial tumours, a fall in insulin could in principle restrain growth [12, 13]. This route is attractive for obesity-related cancers, such as those of the breast, colon and endometrium. It should apply mainly to people with hyperinsulinaemia, though, which may explain why trials in non-diabetic, non-obese populations have been less convincing than the diabetic cohort data. Pollak has pointed out that the direct and indirect mechanisms predict different patient groups and different doses, a distinction that few trials have been designed to test [12].

Randomised evidence has been sparse and, on the whole, sobering. A Japanese phase 3 trial in people without diabetes who had undergone polypectomy found that a low dose of metformin reduced the recurrence of colorectal adenomas and polyps over one year, an encouraging result for prevention that still needs confirmation in larger and longer studies [14]. In advanced pancreatic cancer, adding metformin to gemcitabine-based treatment gave no extra benefit [15]. The

largest adjuvant study, MA.32, randomised thousands of women with early breast cancer and did not show an improvement in invasive disease-free survival with metformin [16]. These results, listed in table 1, do not close the question, but they make a broad treatment effect in unselected patients unlikely.

Table 1: Selected published evidence on repurposed metformin, aspirin and statins in cancer

Agent and setting	Reported finding	Ref.
Observational studies time-related bias	Immortal time and related biases inflated the apparent benefit of metformin in several early cohort analyses	[4, 5]
Metformin cellular mechanism	Inhibits mitochondrial complex I, activates AMPK and restrains mTOR signalling in cancer cells	[6, 7, 9, 10]
Metformin colorectal adenoma	Low-dose metformin reduced adenoma and polyp recurrence after polypectomy in a phase 3 trial of non-diabetic patients	[14]
Metformin pancreatic and breast cancer	No added benefit in advanced pancreatic cancer or in adjuvant breast cancer in randomised trials	[15, 16]
Aspirin colorectal prevention	Long-term low-dose use lowered colorectal cancer incidence and mortality in pooled trial follow-up after a latent period	[17, 18]
Aspirin hereditary risk	Daily aspirin lowered cancer incidence in Lynch syndrome carriers after several years of follow-up	[19]
Aspirin molecular selection	Benefit linked to COX-2 expression and PIK3CA mutation in observational tumour analyses	[20, 21]
Aspirin healthy older adults	No reduction in cancer incidence and a signal of possible harm in people aged 70 and over	[22, 23]
Statins mevalonate pathway	Block cholesterol and isoprenoid synthesis needed for Ras and Rho signalling in tumour cells	[24, 25]
Statins cohort evidence	Lower cancer-related mortality with statin use in registry data and meta-analyses, open to healthy-user bias	[26, 27, 28]
Statins lung cancer trials	Small phase 2 signal with gefitinib; phase 3 pravastatin trial in small-cell lung cancer was negative	[29, 30]

Dose and duration deserve more thought than they usually get. Prevention studies in diabetic cohorts typically reflect years of exposure at 1 to 2 g daily, whereas the polyp trial used a quarter of the usual dose for a short period [4, 14]. Comparing them directly is awkward. In treatment trials the drug has been given alongside cytotoxic chemotherapy, which itself disturbs glucose and insulin handling, so any metabolic contribution of metformin may be harder to detect [15, 16]. Gastrointestinal intolerance also limits exposure, and adherence in a long adjuvant trial is rarely perfect, which pulls a real effect towards the null [16].

3. ASPIRIN

Aspirin is a different kind of repurposing candidate, because its effect on cancer was suspected from its basic pharmacology. By irreversibly acetylating cyclooxygenase, it reduces the synthesis of prostaglandins, and prostaglandin E2 in particular promotes cell proliferation, resistance to apoptosis, angiogenesis and immune evasion in several tumours [31, 32]. COX-2 is overexpressed in most colorectal cancers and many premalignant lesions. Low doses also inhibit platelet activation, which may matter because platelets can shield circulating tumour cells and release growth factors, although that idea is less well proven [31]. A consensus group reviewing the evidence concluded that aspirin was the most promising of the anti-inflammatory drugs for cancer prevention [33].

The trial evidence for colorectal cancer is the strongest in the whole field of repurposing. Cohort data from the American Cancer Society showed that long-term, regular use of adult-strength aspirin was linked to a lower risk of several cancers, but the effect took years to appear [34]. Pooled follow-up of randomised trials, originally designed to study vascular prevention, then showed that allocation to aspirin reduced colorectal cancer incidence and mortality after about ten years,

with the largest benefit in the proximal colon [17]. An individual-patient analysis of the same trials found fewer deaths from several common cancers after a latent period of around five years [18]. Doses in those trials ranged from 75 mg to more than 300 mg daily.

Molecular selection has sharpened the picture. In two large prospective cohorts, regular aspirin use reduced the risk of colorectal cancers that overexpress COX-2, while having no clear effect on tumours with weak expression [20]. After diagnosis, aspirin users whose tumours carried a mutation in PIK3CA lived longer than non-users, whereas wild-type tumours showed no such gain [21]. The two findings fit a coherent biological story, since the PI3K pathway can drive prostaglandin signalling. Both come from observational data, however, and neither has been confirmed in a trial designed around the biomarker. That is why current research focuses on adjuvant studies that select by PIK3CA status, rather than on treating all patients [21].

Hereditary risk provides a clearer test. In the CAPP2 trial, carriers of Lynch syndrome took 600 mg aspirin daily for up to four years, and long-term follow-up showed a substantially lower incidence of colorectal and other Lynch-associated cancers among those who took it for at least two years [19]. The benefit emerged late, in keeping with the pooled trials of average-risk groups [17, 19]. Because the dose used in CAPP2 is larger than the 75 to 100 mg usually taken for vascular protection, a follow-up trial comparing doses has been mounted to find the lowest effective amount, and its answer will matter for the balance of benefit and bleeding [19].

The most awkward evidence came from the elderly. ASPREE randomised more than 19,000 healthy people aged 70 and over, mostly without prior cardiovascular disease, to 100 mg of aspirin or placebo. It found no overall benefit on disability-free survival, and all-cause mortality was slightly higher with aspirin, largely because of cancer-related deaths [22]. A later analysis reported no reduction in cancer incidence and a suggestion that cancers were detected at a more advanced stage among aspirin users [23]. Whether this reflects chance, a different biology of cancer in old age, or an effect that really does depend on starting early is not known, and it counsels caution about extending prevention advice to older people [22, 23].

Timing is the feature of the aspirin data that is easiest to miss. Benefit in the pooled trials appeared only after several years, and it persisted for a long time after the original randomised treatment had stopped, which suggests that aspirin may act by preventing initiation or early growth of lesions, rather than by treating established disease [17, 18]. That pattern argues against short trials. It also helps explain why aspirin has seemed far less impressive when given after a cancer is already present, with the exception of the molecularly defined subgroup described above [21]. For a policy maker the implication is that any prevention programme must plan for a long horizon before benefit is visible [19, 33].

Harms cannot be left out of the balance. Even low-dose aspirin increases the risk of gastrointestinal and intracranial bleeding, and the excess is greater in older people, in those with a history of ulcer and in people also taking anticoagulants or other NSAIDs [22, 31]. For cancer prevention in younger adults with a high baseline risk, the trade is more likely to be favourable than for the general population. Consensus guidance has therefore stressed individualised assessment rather than blanket recommendation, and has proposed that any future prevention programme should be tied to risk stratification [19, 33].

4. STATINS

Statins inhibit HMG-CoA reductase, the rate-limiting step in the mevalonate pathway that Goldstein and Brown described, and that pathway produces not only cholesterol but also isoprenoid intermediates such as farnesyl and geranylgeranyl pyrophosphate [24]. These lipids are attached to small GTPases, including Ras and Rho, which need them to reach the cell membrane and signal. Blocking the pathway can therefore reduce proliferation, migration and survival in cultured cells [24, 25]. Many cancers also depend on the pathway for membrane

synthesis and may upregulate it when mutant p53 is present. That gives a plausible rationale for repurposing, although the sensitivity of tumours to statins varies widely between cell types [25].

Observational data have been generally favourable. A Danish registry study of several hundred thousand cancer patients found that those who had been taking statins before diagnosis had lower cancer-related mortality than non-users [26]. A meta-analysis of 95 cohorts pooled results for many tumour types and reported associations between statin use and better survival, with the strongest signal in some cancers and a weaker one in others [27]. After a diagnosis of colorectal cancer, statin users in a British population-based cohort had a modestly lower risk of death [28]. These findings support a hypothesis, but they are not proof, and the difference between pre- and post-diagnosis use makes comparisons complicated [26, 27, 28].

Interpretation is hampered by the healthy-user effect. People who adhere to statins tend to see their doctor more often, attend screening, and take other preventive steps, all of which can improve survival without any drug action [27]. Statins are also withheld from the frailest patients near the end of life, which is a form of confounding by indication. Some studies try to reduce this by using lag periods and cumulative-dose analyses, and these typically yield smaller effects than simple ever-never comparisons [5, 27]. The Danish study partly addressed the problem by examining use before diagnosis, but it cannot exclude residual confounding [26]. A causal effect remains plausible, not proven.

Trials in established cancer have been disappointing so far. A randomised phase 2 study of simvastatin added to gefitinib in advanced non-small-cell lung cancer suggested a possible gain in response in selected patients, but it was small and its subgroup findings were not confirmed [29]. The much larger LUNGSTAR trial added pravastatin to chemotherapy in small-cell lung cancer and found no improvement in overall survival [30]. One possible explanation is the choice of statin, since lipophilic compounds such as simvastatin penetrate tissues more readily than hydrophilic ones like pravastatin. Another is that patients with advanced disease may simply be too late for an agent that is better suited to slowing initiation or early progression [24, 30].

Tumour genetics may decide who is sensitive. Cells with mutant p53 can drive the mevalonate pathway through sterol regulatory element binding proteins, and such cells appear unusually dependent on it for growth and for maintaining a malignant phenotype [25]. Statin sensitivity in the laboratory also tracks with how much a cell relies on geranylgeranylation of small GTPases, rather than with cholesterol content alone [24, 25]. If these findings hold in patients, the right trial population would be defined by tumour biology instead of by tumour site, which is a different design from anything tested so far, and one that would need tissue sampling to be built into routine care. It is a good example of how mechanism could, in principle, rescue a drug that looks flat in unselected cohorts [27, 30].

Pharmacological differences within the class may explain some inconsistency between studies. Lipophilic statins such as simvastatin, atorvastatin and lovastatin enter cells by passive diffusion and reach extrahepatic tissues readily, whereas hydrophilic agents such as pravastatin and rosuvastatin depend on hepatic transporters [24, 25]. Several preclinical studies find stronger antiproliferative activity with the lipophilic group, and cohort analyses sometimes show larger associations with them, though the data are not consistent [27, 28]. Trials that have used a single agent therefore say little about the class as a whole. Differences in half-life, potency and drug interactions, for instance with agents handled by CYP3A4, add a further layer of variation that rarely appears in cohort analyses [27, 29, 30].

5. COMPARING THE EVIDENCE

Putting the three drugs side by side shows how unevenly the evidence is distributed. Aspirin has trial support for prevention in two settings, average-risk adults followed for many years and carriers of Lynch syndrome, but contrary evidence in the very old [17, 19, 22]. Metformin has biologically rich

mechanistic work and an encouraging polyp-prevention trial, yet its treatment trials were negative [7, 14, 15, 16]. Statins have the largest observational base and the weakest trial base [26, 27, 30]. The main findings are summarised in table 1, and the number of entries per category is shown in fig. 1.

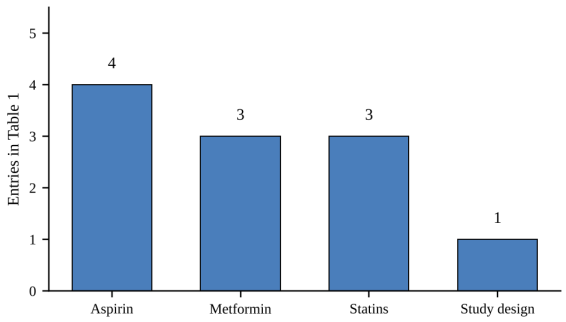


Fig. 1: Number of entries in table 1 by drug and evidence category

Several themes cut across the drugs. First, benefit appears to be greatest when the drug is started early and taken for years, which makes trials expensive and slow. Second, biological selection, whether by COX-2 expression, PIK3CA mutation or LKB1 status, may separate responders from non-responders more effectively than clinical features do [9, 20, 21]. Third, the endpoint matters, because a drug that prevents adenomas need not improve survival once a carcinoma has formed [14, 16]. Fourth, observational estimates of any of these drugs should be read with the design problems described by Suissa and Azoulay in mind, and not as a ranking of efficacy [5].

Safety in people who already have cancer is a separate issue from safety in healthy users. Metformin is cleared by the kidneys and is avoided when renal function is poor, a situation that is common after platinum chemotherapy, and gastrointestinal side effects can compound those of cytotoxic drugs [11, 15]. Aspirin adds to the bleeding tendency of thrombocytopenia and of anticoagulation, so it requires closer thought in haematological and advanced solid tumours [22, 31]. Statins share metabolic pathways with some targeted therapies and may interact with them, and muscle symptoms can be confused with treatment toxicity [29, 30]. None of this prohibits trials, but it does shape their eligibility criteria.

6. LIMITATIONS AND FUTURE DIRECTIONS

This review is narrative and draws on a selection of influential studies, so it is open to selection bias, and it does not offer a quantitative synthesis. Many of the cited studies used different doses, populations and endpoints, and some of the strongest claims rest on a single cohort. Time-related bias remains the most important methodological hazard in the observational literature, and analyses that handle it poorly will overstate benefit [5]. Publication bias probably favours positive findings in the early metformin and statin cohort papers [4, 27]. Readers should regard the associations described here as hypothesis-generating unless a randomised trial supports them.

Several directions seem worth pursuing. Biomarker-driven adjuvant trials, such as aspirin in PIK3CA-mutated colorectal cancer, would test the most coherent hypothesis currently available [21]. Dose-finding studies in aspirin chemoprevention could reduce harm while keeping benefit [19]. For metformin, trials stratified by insulin status, body weight and tumour metabolism are more likely to be informative than further studies in unselected groups [12, 16]. For statins, the choice of agent and the timing of exposure should be built into the design [24, 30]. Pragmatic, registry-based trials might lower cost, which is the main reason these questions have stayed open for so long [1, 2].

7. CONCLUSION

Metformin, aspirin and statins illustrate both the promise and the limits of repurposing in oncology. Aspirin is the clearest success, with trial-based support for colorectal cancer prevention, especially in Lynch syndrome, though bleeding risk and the findings in healthy older adults temper enthusiasm [17, 19, 22, 23]. Metformin has persuasive laboratory biology and one positive prevention trial, but treatment trials in established cancer were neutral [7, 14, 15, 16]. Statins carry a large observational signal that has not yet been matched by randomised data [26, 27, 30]. Across all three, the gap between a biologically attractive mechanism and a patient-level benefit has proved wider

than early enthusiasm assumed [7, 12].

Taken as a group, these drugs are better regarded as candidates for selected populations than as general anticancer agents. Progress will probably depend on biomarkers, early intervention, sensible dosing and trial designs that avoid the biases that distorted the first cohort studies [5, 12, 21]. Clinicians should not prescribe any of the three for cancer outside a trial or an established indication, and patients who take them for diabetes, vascular disease or lipid control can be told that a possible additional benefit is plausible but unproven [1, 2, 3, 33].

8. ABBREVIATIONS

AMPK-AMP-activated protein kinase, mTOR-Mechanistic target of rapamycin, COX-2-Cyclooxygenase-2, HMG-CoA-3-Hydroxy-3-methylglutaryl coenzyme A, NSAID-Non-steroidal anti-inflammatory drug, ATP-Adenosine triphosphate, PIK3CA-Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, LKB1-Liver kinase B1

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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