The Tumour and the County

The cause of cancer and the cure for cancer are being pursued as two separate problems. They are currently failing for one reason, at two scales: in both, the field reports an average over a population that contains effects running in opposite directions, and in both, the measurement that would separate them already exists in data already collected. This essay sets out what the available numbers support, what they do not, and which measurement would settle the difference.

J. Konstapel, Constable Research, Leiden — 31 October 2026

What is claimed here and what is not

This essay does not claim to give the cause of cancer or a cure for it. Anyone offering either from the present evidence is overreaching, and the sections below say where the evidence stops.

What is claimed is narrower and, if correct, more useful.

First, that the accumulation of driver mutations cannot by itself be the cause, because driver mutations are not scarce. By middle age they are the majority condition of some normal tissues, and at least one classical driver is commoner in healthy tissue than in the cancer named after it. The scarce ingredient is something else.

Second, that removal, the operation on which the therapeutic effort rests, has a ceiling that is structural rather than technical, and that this is visible inside a single patient over eighteen months rather than inferred.

Third, that the largest measured lever on cancer is not therapeutic at all, and its size is known: 40.0% of cases in United States adults aged 30 and over are attributable to exposures that can be removed from the environment rather than from the body.

Fourth, and this is the organising claim, that the cause question and the cure question are failing for the same reason. Both are currently answered with an average taken over a population that contains effects running in opposite directions. In the clinic that population is a trial arm; in epidemiology it is an occupation or a county. In both, the measurement that would separate the halves exists in data already collected, and in both, nobody has separated them.

What this essay cannot supply is the one thing cancer most needs and the other fourth-row diseases now have: a measured boundary marker. Sepsis has suPAR, acute respiratory distress has a baseline inflammatory classification, atherosclerosis has hsCRP. For cancer there is no equivalent proposed here, and naming it is the open problem rather than a gap in the writing.

Removal has a ceiling, and it is visible in one body

There are four ways a disease state ends. It resolves on its own. One of two parties is removed. Something missing is supplied. Or both parties remain, the relation between them does not settle, and what must change is the proportion.

Oncology is organised almost entirely around the second. The question is how far it reaches.

FLAURA gives the cleanest answer available, because it tested the best first-line removal agent in its class against the previous generation in EGFR-mutated non-small-cell lung cancer. Median progression-free survival was 18.9 months against 10.2, a hazard ratio of 0.46, close to a doubling. Median overall survival was 38.6 months with a confidence interval of 34.5 to 41.8, against 31.8 with 26.6 to 36.0, a hazard ratio of 0.80 at P = 0.046. That is 6.8 months. At three years, 28% of patients were still on the regimen, which is to say 72% were not.

The distance between those two figures is the finding. The time before return nearly doubles; survival gains a fifth; and nearly three quarters of patients have left the treatment within three years. What is removed is removed. What remains is what the removal did not reach, and what remains is what continues.

This is the same shape as antimicrobial resistance, where deaths directly attributable to bacterial resistance are forecast to rise from 1.14 million in 2021 to 1.91 million in 2050. The difference is scale: in infection the escape is selected across a population over decades, in oncology inside one body over eighteen months. The mechanism of the ceiling is identical and it is not a property of the compound. Removing a self-replicating party selects for whatever was not removed.

So cancer is not an instance of the second operation awaiting a better molecule. Nothing foreign is present and nothing is missing. What does not settle is division itself, which places it structurally in the fourth row, with sepsis, acute respiratory distress, the autoimmune diseases and atherosclerosis.

That placement is an argument from the shape of the failures, not a demonstration, and the next sections test it against the causal evidence rather than assuming it.

The same averaging error, at the scale of a county

Iowa has had the second-highest cancer incidence in the United States for three consecutive years, behind Kentucky, and is the fastest-rising state while national rates fall. The Iowa Cancer Registry projects about 21,700 diagnoses and about 6,400 deaths there in 2026. The state is agricultural, and the public argument is that agricultural chemistry is the cause.

The registry's own March 2026 report tested that where it is most testable. Comparing Agricultural Health Study farmers with the general Iowa population over 1994 to 2015, adjusted for age and sex, farmers had 13% fewer cancers than expected. Their spouses had 10% fewer. The most exposed group had less cancer than the population around it.

That figure is now quoted on both sides of a political argument, and it should not be quoted by either, because it is an average of two opposite things. Taken apart by site:

Direction	Sites
Lower than expected in farmers	Colon and rectum, lung, bladder, oral cavity and pharynx, pancreas, oesophagus, larynx, liver, tongue
Higher than expected in farmers	Prostate, about 20% above expected; lip, about 65% above expected
Higher than expected in spouses	Melanoma, thyroid

Every one of the nine sites that came in low is a site associated with tobacco, alcohol, or both. The registry attributes the deficit to exactly that, lower smoking and drinking, together with the tendency of physically demanding work to be done by healthier people. The two sites that came in high are the two that are not driven down by abstinence: lip, where outdoor work and smokeless tobacco are the candidates, and prostate, which is where the exposure signal in this population actually sits.

So a large behavioural deficit has been averaged against a specific exposure excess, and the result is reported as a single number that supports neither conclusion. This is the error that RECOVERY made with dexamethasone, where the pooled estimate concealed a stratum in which the drug ran against the patient, and that HARP-2 made with simvastatin, where a benefit confined to one baseline class was averaged into a null. The difference is only that here the strata are tissues rather than patients.

Two honest cautions belong with this. The cohort has aged, many participants stopped farming years ago, and Iowa has no good system for tracking which compounds are in use now, so the comparison speaks to past exposure rather than present. And melanoma and thyroid, the two sites elevated among spouses, are the two cancers most sensitive to increased detection, which makes that particular excess hard to read. The second point is an inference from what is known about those cancers generally, not a finding of the report.

One gradient worth measuring, one deadlock worth leaving

The practical question is not whether agriculture causes cancer. It is which exposure, at what measured level, in which tissue. On that question the Iowa evidence splits sharply into one tractable case and one exhausted one.

Nitrate is the tractable case. In this same study population, drinking-water nitrate above 10 mg/L is associated with increased risk of aggressive prostate cancer, and ovarian cancer risk rises with average nitrate concentration. Prostate is also the site that stands out among the farmers. Three things therefore exist at once, which is rare: a measured exposure gradient, because nitrate is assayed per public water supply; a proposed threshold, at 10 mg/L; and a complete population cancer registry covering the same geography over decades. The stratifier, the dose and the outcome are all already collected, by different institutions, and have not been put together.

Glyphosate is the exhausted case, and the reason to say so is that the spread across analyses is now larger than any effect they are arguing about.

Analysis	Risk estimate for non-Hodgkin lymphoma
Zhang 2019, fixed effect	1.41 (1.13 to 1.75)
Zhang 2019, random effects	1.56 (1.12 to 2.16)
Agricultural Health Study, highest quartile, 20-year lag	1.12 (0.83 to 1.51)
EPA meta-analysis including that study, random effects	1.14 (0.87 to 1.50)
High-quality studies only	1.03 (0.61 to 1.75)
AGRICOH pooled, all non-Hodgkin lymphoma	0.95 (0.77 to 1.18)
AGRICOH pooled, diffuse large B-cell subtype	1.36 (1.00 to 1.85)

The Agricultural Health Study, the largest and highest-quality contributor with 575 cases, showed no significant association across exposure quartiles and no trend, at P = 0.62. The 1.41 figure was reached by choosing a fixed-effect model and by taking only that study's highest-exposure quartile, whose own estimate is 1.12 with an interval crossing 1. The International Agency for Research on Cancer classifies glyphosate as probably carcinogenic; the

Environmental Protection Agency concludes it is not likely to be carcinogenic to humans. Both institutions have read the same papers.

The county-level maps now circulating do not break that deadlock and cannot. The analysis most cited in the current Iowa campaign is a map overlay by an advocacy organisation: 82% of Iowa's heaviest-spraying counties lie above the national lymphoma average and 50% are hot spots. It reports no effect size, no confidence interval and no adjustment for age, smoking or other compounds; 31% to 42% of counties were dropped for missing outcome data; and glyphosate use was estimated from agricultural statistics rather than measured. Herbicide is applied where row crops are, which is also where the age structure, the radon, the nitrate and the farming population are. A map cannot separate those, and a conclusion drawn from one is the same pooled error a third time, in cartographic form.

The recommendation that follows is unglamorous. Leave the glyphosate question to the institutions already locked on it, and spend the available effort on the exposure that has a number, a threshold and a registry.

Driver mutations are not the scarce ingredient

The standard causal account is that cancer arises when a cell accumulates enough driver mutations. That account predicts that driver mutations should be rare in healthy tissue. They are not.

In normal eyelid skin, positively selected driver mutations were found in 18% to 32% of cells, at a density of about 140 per square centimetre, with a burden of 2 to 6 mutations per megabase per cell. NOTCH1 mutations were carried by an estimated 14% to 21% of skin cells, TP53 and FAT1 by 3% to 5%. The authors describe aged skin as a patchwork of thousands of evolving clones, with over a quarter of cells carrying cancer-causing mutations, and note that sequencing established cancers shows only the winners of a process that must be observed in normal tissue to be understood.

The oesophagus is more striking. In tissue from nine people aged 20 to 75, none with any history of oesophageal cancer, more than half of the normal epithelium had been taken over by mutant clones by middle age. Mutation burden ran from several hundred per cell in people in their twenties to over 2,000 later in life.

And within that one tissue, two classical drivers behave in opposite directions.

Gene	In normal oesophagus	In oesophageal cancer
TP53	5% to 10% of cells	almost all cancers

Gene	In normal oesophagus	In oesophageal cancer
NOTCH1	nearly half of all cells by middle age	several times less common than in normal tissue

TP53 behaves as the accumulation account requires: uncommon in healthy tissue, near-universal in the disease. NOTCH1 behaves backwards. A mutation that is several times more frequent in healthy oesophagus than in oesophageal cancer cannot be, on its own, a step toward that cancer. The investigators raise the possibility that it protects, and are careful to present that as a possibility rather than a finding.

What the two results establish together is narrower than a refutation and more useful than one. Driver mutations are not scarce, so their presence is not what is scarce. By middle age a normal oesophagus is mostly mutant clones that stay a normal oesophagus. Something continues to hold them in the tissue, and in the overwhelming majority of people it continues to do so for a lifetime.

That is the fourth-row statement arrived at from the causal side rather than asserted from the therapeutic one. What does not settle is division; the mutation is the occasion and not the cause; and the question to put to the tissue is not how many drivers a clone carries but what decides whether it keeps settling.

The limits are real and should be stated with the finding. These are small studies: nine individuals for the oesophagus, a single tissue type in each case. They are cross-sectional surveys of normal tissue, not a follow-up of clones into malignancy. None of this refutes the somatic mutation theory of cancer. It refutes the sufficiency of counting mutations, which is a different and narrower thing, and it is the part that the research programme has been built on.

The one removal with no ceiling

Removal fails inside the body because what is removed selects for what was not. That failure has a precondition: the party being removed must be able to change. An exposure in the environment cannot. Nitrate does not acquire resistance to a catchment rule, and tobacco does not evolve around a tax.

So the fourth row's logic produces an unexpected conclusion about the second. There is exactly one application of removal in cancer with no structural ceiling, and it operates before the disease rather than on it.

Its size is measured. In United States adults aged 30 and over in 2019, excluding non-melanoma skin cancer, 713,340 of 1,781,649 cases were attributable to potentially modifiable risk factors, which is 40.0%, and 262,120 of 595,737 deaths, which is 44.0%.

Factor	Share of cases	Attributable cases
Cigarette smoking	19.3%	344,070
Excess body weight	7.6%	135,910
Alcohol consumption	5.4%	96,730
Ultraviolet radiation	4.6%	82,710
Dietary factors	4.2%	—
Infections	3.4%	—
Physical inactivity	3.1%	—

Smoking, excess weight and alcohol together account for 32.3% of all cases, which is 81% of the attributable 40%. For deaths, smoking alone accounts for 169,810 of the 262,120 attributable, which is 65%.

Three things follow, and the third is the one that matters for Iowa.

The lever is larger than anything in the therapeutic pipeline. No agent in development will move 40% of incidence, and the comparison is not close.

It does not require the causal question to be settled first. An attributable fraction is a counterfactual about removing an exposure, and removing tobacco does not wait on knowing which mutation it produced in which cell.

And it reorders the Iowa argument. The registry names binge drinking among the worst in the nation and a cigarette tax unchanged for nearly twenty years, in a state rated high-risk for radon throughout. Those are the three factors with the largest measured attributable fractions, they are the ones the farmer data points at through the nine sites that came in low, and they are almost entirely absent from the public argument, which is about herbicide. The exposure with the strongest evidence and the largest lever is the one nobody is campaigning on, because it implicates the electorate rather than an industry.

None of which says agricultural exposure contributes nothing. It says that the order of attention is inverted, and that the attributable fractions are the measurement that inverts it.

Where the work should go

Six directions follow from the above. None of them requires a discovery, and three require no new data collection at all.

#	Direction	What is built	Judged by
1	Report occupational and geographic cancer comparisons by site, never pooled	Site-level tables as the default output of a registry comparison	Sign reversals visible rather than averaged away
2	Link the nitrate gradient to the registry	A cohort analysis using measured water-supply nitrate as the exposure and the 10 mg/L threshold as the stratifier	Dose-response by site, prostate first
3	Stop funding ecological map overlays as evidence	Nothing; the saving is the point	Claims withdrawn from the public argument
4	Study normal tissue, not only tumours	Longitudinal surveys of mutant clone behaviour in healthy tissue across exposures	Which clones stop settling, and on what
5	Name a boundary marker for cancer	A measurable quantity dividing clones that continue from clones that do not	Prospective separation before any intervention

#	Direction	What is built	Judged by
6	Spend the prevention budget in proportion to the attributable fractions	Tobacco, weight and alcohol policy at the measured 32.3% of cases	Incidence, not awareness

Direction 5 is the one that matters most and the one with nothing behind it yet. The other fourth-row diseases became tractable the moment somebody named a marker: suPAR at 6 ng/mL for sepsis, a baseline inflammatory class for acute respiratory distress, hsCRP at 2 mg/L for atherosclerosis. In each case the marker did not explain the disease; it divided the population into halves in which the same intervention ran in opposite directions, and that was enough to recover effects that pooled trials had discarded.

Cancer has no such quantity proposed. The nearest thing the evidence here suggests is not a property of the tumour but of the tissue around it: whatever distinguishes a normal oesophagus that is mostly mutant clones and stays normal from one that does not. That is a measurable question and nobody is measuring it, because the field surveys tumours, which are the clones that already stopped settling.

Direction 2 is the one that could be started this quarter with no new fieldwork. Iowa holds a complete population cancer registry going back decades, and nitrate is assayed per public water supply across the same geography. Linking them is a records exercise. If the association with aggressive prostate cancer above 10 mg/L holds in the full registry rather than in a cohort, that is an exposure with a threshold, which is the first thing in this entire argument that a regulator could act on.

Verification and limitations

Every figure was recomputed from the reported counts or percentages before being quoted.

Check	Recomputed	As reported
Attributable cases, US adults 30+	713,340 / 1,781,649 = 40.0%	40.0%
Attributable deaths	262,120 / 595,737 = 44.0%	44.0%

Check	Recomputed	As reported
Smoking share of cases	344,070 / 1,781,649 = 19.3%	19.3%
Smoking, weight and alcohol combined	19.3 + 7.6 + 5.4 = 32.3% of all cases	not stated
That combination as a share of the attributable total	32.3 / 40.0 = 81%	not stated
Smoking share of attributable deaths	169,810 / 262,120 = 65%	not stated
FLAURA progression-free survival	18.9 / 10.2 = 1.85-fold, +8.7 months	HR 0.46 (0.37 to 0.57)
FLAURA overall survival	38.6 / 31.8 = 1.21-fold, +6.8 months	HR 0.80, P = 0.046
FLAURA patients off the regimen by 3 years	100 minus 28 = 72%	28% still on regimen
Iowa deaths against diagnoses, 2026 projection	6,400 / 21,700 = 29.5%	21,700 and 6,400
AMR attributable deaths, 2021 to 2050	1.14 to 1.91 m, +67.5%	+67.5%
Iowa farmer sites running low	9 of 9 tobacco or alcohol associated	deficit attributed to smoking and drinking
Glyphosate estimates, spread across analyses	0.95 to 1.56	see the table above

Limitations. The attributable-fraction estimates are counterfactual modelling, not experiments, and they depend on assumed exposure prevalences and relative risks; they are United States figures and do not transfer to Iowa or to Europe unchanged. The normal-tissue mutation studies are small, nine individuals for the oesophagus, and cross-sectional: they observe clones at one moment and do not follow them into malignancy, so the claim that NOTCH1 protects remains the investigators' stated possibility rather than a result. The Iowa farmer comparison is against the general state population rather than against matched non-farmers, the cohort has aged out of

current exposures, and the healthy worker effect is acknowledged by the registry itself rather than adjusted away. FLAURA compares against first-generation inhibitors rather than against no removal, and crossover was permitted, so its survival difference understates the agent while saying nothing about whether removal was the right operation. The placement of cancer in the fourth row is an argument from the shape of its failures and from the normal-tissue evidence, not a demonstration, and this essay proposes no boundary marker, which is the test it would have to pass. And the four-operation scheme is exhaustive by construction, so it cannot be refuted as a scheme; what is refutable is every row assignment in it, including this one.

Sources

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- GRAM Project forecasts of antimicrobial resistance mortality, University of Oxford.

Framework and companion essays

- J. Konstapel, *Research Directions to Cure All Diseases*, Constable Research, Leiden, 29 October 2026 - the four operations and the ten directions.
- J. Konstapel, *The Order of Questions*, Constable Research, 30 October 2026 - the ordering of marker, endpoint and agent, and the six gates.
- J. Konstapel, *Depth of Discharge*, Constable Research, 29 October 2026 - the stratification argument in full.
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