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REVIEW

BEYOND TARGETED THERAPY: ENVIRONMENTAL DETERMINANTS AND METABOLIC STRATEGIES IN CANCER PREVENTION AND TREATMENT

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ABSTRACT: Despite significant advances in cancer care, cancer remains the second leading cause of death in the USA. For a cost-effective initiative to decrease cancer incidence, we argue in this review that an understanding of modifiable environmental factors in cancer and risk mitigation strategies should come first, as a population health approach to cancer. Additionally, this review also motivates the development of broad spectrum metabolic approaches to cancer, which may be effective over a broad array of cancers, instead of current antineoplastic agents, which are targeted against a small subset of cancers. By using a preventative approach, as well as utilizing low cost and broad spectrum therapeutic agents, it may be possible to improve cancer outcomes without a significant increase in cost. This review provides a roadmap for environmental risk mitigation as well as adjunctive, broad spectrum therapeutics.

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Impact statement: This review assesses the feasibility of generalist approaches to cancer care, which may be helpful to a broad swathe of the population.

Key words: *Cancer; metabolic therapy; environmental factors; warburg effect; ketogenic diet.*

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INTRODUCTION

While the burden of preventable disease declines with advances in sanitation, public health, and economic development, cancer remains a major global challenge, currently accounting for about 0.55% of global GDP in expenditures (1). Cancer incidence is influenced by several factors, environmental factors are associated with cancer incidence and may explain some of the trends in cancer (2).

Most prosaically, mortality from other diseases is dropping, and so as lifespan increases, people are more prone to get cancer, as cancer's incidence rises with age(3). Early stage screening has also contributed to lowered cancer mortality (4, 5), and treatments for some specialized cancers have decreased the overall mortality burden of cancer (6).

While most cancers are due to mutations acquired over the lifespan, inherited genetic factors play a significant role in cancer development in a proportion of total cancers. It is estimated that between 5 and 10% of all cancers are associated with an inherited mutation (7). The wider prevalence of genetic testing may inform people of their cancer risk predisposition, which may provide actionable information in specific cases (8).

Diet is a significant factor in cancer incidence (9). Ultra processed food (UPF) consumption is associated with elevated cancer risk (10). There are multiple pathways by which ultra processed foods can contribute to cancer incidence (11), though broadly, these are high in calories (12) and unhealthy fats (13), have low nutrient content (14), and may contain additives including preservatives (15) and emulsifi-

ers (16). The increased palatability of UPFs makes it easier for people to overeat (17), which can contribute to metabolic conditions and obesity (18), increasing cancer risk (19).

Besides micronutrients, UPFs also are lower in phytonutrients (20), and regular consumption has negative impacts on the gut microbiota (21), as UPFs are typically lower in fiber (22). Micronutrients (23), phytonutrients (24), probiotics (25), and prebiotic fiber (26) demonstrate anticancer associations in epidemiological studies. Micronutrient consumption is associated with overall health (27), and can be important in the context of cancer. Dietary nutrient density per calorie is inversely associated with cancer risk (28).

Packaging (29) and additives represent another dimension in which UPFs differ from unprocessed foods. Additives, while not a significant source of nutrition, being present in small amounts, may have health effects, though any toxicity typically manifests at consumption levels far above what consumers would be exposed to. Producers include additives to alter the texture, appearance, material properties, or extend the shelf life of a food product. EU regulation defines 27 categories of food additives, including sweeteners, flavor enhancers, emulsifiers, colorants, preservatives, and stabilizers (30) (**Supplementary Table 1**). While it is difficult to characterize the toxicological profile of the wide variety of food additives (The Food and Feed Informa-

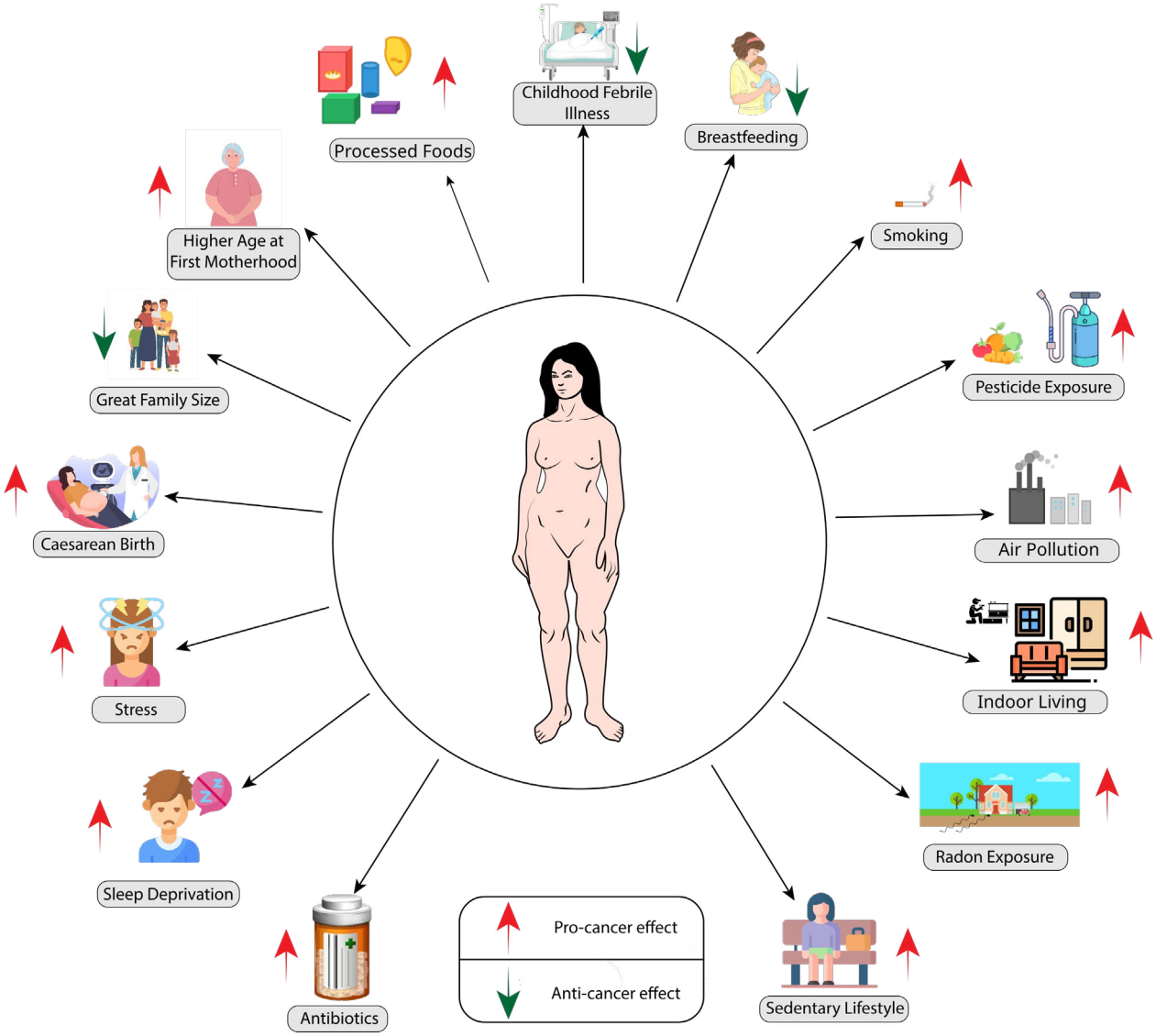

Figure 1. *Epidemiological factors and their impact on cancer incidence.*
Green downward arrows mean that the factor is associated with lower rates of cancer, whereas upward red arrows mean that the factor is associated with an increased risk of cancer.

tion Portal of the European Commission lists 412 unique food additives in its Version 5.6.0 Database, accessed February 11, 2026) (31) in the limited space of this review, it is important to note that some additives have been regulated or face restrictions owing to observed toxicity (32), sometimes in the form of carcinogenicity (33), albeit typically out of an abundance of caution.

Beyond ultra processed food, even whole foods contain pesticide residues and have lower nutrient densities than their counterparts of a few decades past, and are novel on the time scale of human evolution (34).

Beyond diet, environmental exposures may mediate cancer risk (35); these are outlined in **Supplementary Table 2** and **Figure 1** of this article.

Lifestyle factors

Physical activity, sleep, and stress

Modern humans spend most of their life indoors and increasingly live sedentary lives, as more people are employed in the information economy and spend most of their working day using a computer (36). While increasingly, standing desks and even treadmill desks are being used (37), still, the levels of physical activity have decreased. Physical activity has many anti-cancer effects, and exercise is associated with a lowered risk of cancer development (38).

Poor sleep quality and short sleep duration are another contributor to cancer and ill health in general (39). Devices and lights can disrupt sleep and artificial light at night (ALAN) can disrupt melatonin production and result in poorer sleep quality and duration (40).

Chronic stress is another contributor towards lower quality of life and may play a role in cancer progression (41). These factors are also interacting, as stress (42) and poor sleep (43) can induce cravings for sugary food.

Microbiome

A healthy and diverse gut microbiome is associated with a lower cancer risk, and perturbations are associated with the cancer phenotype (44). Several factors have altered human gut bacterial composition over millennia, including a lower exposure to microbes in the environment, greater hygiene, and the increased use of antibiotics and birthing via caesarean section (45).

The number of antibiotic prescriptions has declined in recent years (46, 47). Antibiotics necessarily depopulate the gut microbiome, and can lead to dysbiosis (48, 49). Among other conditions (50, 51), antibiotic use is associated with an increased rate of colorectal cancer (52) and other cancers (53).

Family size

Children born into larger families are less likely to develop allergies, which can serve as a proxy for gut health (54). Number of older siblings is negatively associated with risk of Hodgkin's Lymphoma (55), acute monocytic leukemia and childhood acute lymphoblastic leukemia (56). However, this benefit accrues to the younger siblings, and having four or more total siblings was associated with greater rates of multiple myeloma, acute monocytic leukemia and childhood acute lymphoblastic leukemia (56). Interestingly, number of siblings was positively associated with gastric cancer risk (57). Childhood febrile illness is also associated with a lower risk of cancer later in life (58).

Changing reproductive norms

When babies are born vaginally, they are coated with the vaginal fluid of the mother, which provides colonization for the baby's microbiome (59); without this initial influence, gut dysbiosis in the newborn can occur (60, 61). It is observed that children born via cesarean section have higher rates of autoimmune disorders (62), allergies (63, 64), respiratory diseases (65), and cancers (66-68).

Another reproductive factor, the increasing age at first birth (69), can have an impact on breast cancer risk, as women who are under 25 when their first baby is born have a 35% reduction in their breast cancer risk (70). The use of hormonal birth control is also associated with a higher risk of breast cancer (71), and hormonal birth control is ubiquitous, with one in four US women aged 15-44 using oral contraceptives in a survey between 2011 and 2013 (72).

Environmental exposures

Pesticides

Two developments mark distinct turning points in agricultural technology, the development of the Haber-Bosch process in the early 1910s for producing fertilizer, and the production of synthetic pesticides in industrial quantities, enabling agricultural production on a much larger scale. While some synthetic chemical pesticides were used in the 19th centuries, production and use reached an

inflection point in the 1940's (73). Before the widespread use of pesticides, much of agriculture would be considered organic by today's standards (74), as synthetic fertilizers and pesticides were not widely available.

These developments are important for two reasons, as synthetic fertilizers have contributed to soil micronutrient loss (75), and conventional farming practices can contribute to lower nutrient levels when compared to organically grown foods (76). Secondly, exposure to synthetic pesticides is carcinogenic in many cases (77-79). Other chemical applications may also have negative impacts on health, such as glyphosate used as a wheat desiccant and in the harvesting process (80).

Synthetic pesticide uses also saw another inflection point in the 1990's, with the development of roundup ready soybeans and corn, for use with the pesticide glyphosate (81). Glyphosate was first commercialized in 1974 and worldwide consumption has increased drastically from 56 thousand tons in 1994 to 825 thousand tons in 2014, an almost 15 fold increase (82). The genetic modification process involved inserting a gene for glyphosate resistance, found in a species of plants, into the genomes of soybeans, corn and cotton to enable glyphosate resistance (83). This allowed 'Roundup-Ready', or glyphosate resistant crops to tolerate glyphosate, and the surrounding weeds, lacking the resistance gene to glyphosate, would perish (84).

Unfortunately, glyphosate resistant weeds have emerged (85), and so other strategies are being employed, including using multiple pesticides in combination. With regards to the former approach, multi-pesticide resistant weeds have also emerged, and an arms race is in progress between weeds and pesticides (86).

Meta-analyses have found occupational exposure to glyphosate is associated with an increased risk of non-Hodgkin's Lymphoma (NHL) (87, 88), though this may be confounded by the co-presence of other pesticides (87) or socioeconomic factors (89).

Built environment

Materials used in the built environment have carcinogenic potential (90). As people spend the majority of their lives indoors, exposure to building materials is more significant, including natural radiation (91). Radon contamination from the natural environment is common in residential buildings, and high radon exposure is associated with a higher risk of lung cancer (92).

Air pollution is associated with higher rates of lung cancer (93), and it is estimated that globally, air pollution is responsible for hundreds of thousands of lung cancer cases annually (94).

CHANGING PARADIGMS IN CANCER TREATMENT

Oncology has been characterized by an implicit somatic mutation theory of cancer, whereby mutations in precancerous cells result in the deactivation of the hallmarks of normal cells. The hallmarks of cancer cells have been described in an oft-cited review by Hanahan and Weinberg in 2000, where cancer has the following characteristics (95):

1. Sustaining proliferative signaling
2. Evading growth suppressors
3. Resisting cell death (apoptosis)
4. Enabling replicative immortality
5. Inducing angiogenesis
6. Activating invasion and metastasis

These hallmarks were amended in 2011 to add two additional general hallmarks: reprogramming of energy metabolism and evading immune destruction (96). Metabolic reprogramming refers to the switch from oxidative phosphorylation method of energy production to fermentation, even in the presence of oxygen, a phenomenon known as the Warburg effect (97). The metabolic switch is not unique to cancer, as it has been observed in rapidly dividing embryonic tissue.

This framework has played a role in the comprehension of how numerous tumors assist in quick proliferation and biosynthesis, though it must be critically understood that not all tumor types, stages, and microenvironments necessitate uniform metabolic dependencies (98, 99). Practically, tumors can be highly heterogeneous with regard to metabolism and may alternate between glycolytic and oxidative phosphorylation, as well as alter their state in response to oxygen and nutrient levels (97).

From a cellular energetics perspective, fermentation is an inefficient process, producing 2 ATP per molecule of glucose as opposed to the 38 ATP of the standard oxidative phosphorylation glycolytic pathway (100). Intense exertion can create transient hypoxia within the cell, and the cell can briefly switch to fermentation while lifting a heavy load or other intense exercises (101, 102).

This increased fermentation of glucose increases levels of lactic acid, a byproduct of fermentation, in the tumor microenvironment. This lowers the pH in the extracellular environment and further potentiates the evolution of the surrounding cells to be metastatic, to escape the acidic conditions (103). This increased acidity also decreases the structural integrity of the extracellular matrix holding the cells together, further contributing to metastasis (104).

Given that cancer cells preferentially consume glucose, several researchers have investigated metabolic approaches to differentially target cancer cells, without adversely impacting healthy cells. The metric used is typically the selectivity ration, or the ratio of the inhibitory concentration (to kill 50% of cells in a given sample) in cancer cells to that of normal cells (105).

Lower selectivity results in more toxicity for the patient, though drug selectivity can be improved via sensitizing approaches, which make the cell more vulnerable to a stressor, such as radiotherapy, reactive oxygen species, or chemotherapy. Meanwhile, tumor metabolism also should not be over-simplified into the idea that the deprivation of glucose will always effectively starve tumors and leave normal tissue unaffected, as cancers may evade glucose depletion (106, 107). Even though cells under normal conditions tend to have preserved metabolic flexibility, tumors themselves tend to develop and evolve in a nutrient-restricted microenvironment, including, but not limited to, comparatively glucose-poor regions (108). This leads to the tumor cells being able to develop compensatory survival mechanisms, including more intensive use of alternative substrates, adaptive stress programs including nutrient scavenging behavior (*e.g.*, macropinocytosis), cell recycling pathways (*e.g.*, autophagy) (109), and, under certain conditions, consumption by other cells (*e.g.*, cannibalism-like feeding) (110). As such, glucose restriction should be portrayed as a context-dependent intervention as opposed to a universally selective or universally cytotoxic intervention, and any assertion of extraordinarily high selectivity must be viewed with a degree of caution and must also be correlated to tumor type, microenvironmental conditions, and other stressors (111). Even normal cell functioning can be enhanced during low-glucose conditions (112).

Multidrug combinations have enabled oncologists to lower the doses of drugs in some circumstances, resulting in a better overall toxicity profile for the patient. While this approach lessens the likelihood of drug resistance (113, 114), multidrug resistance is a common occurrence, and cancers can re-emerge after treatment (115).

Drug resistance is a challenge in oncology, which can be addressed via multidrug cocktails. These combinations of anticancer agents attack the cancer cell by multiple pathways such that it is less likely to survive and develop resistance (113, 114). Additionally, reductions in tumor size must be treated with caution, as while some of the pathological impacts of the tumor may be ameliorated, cancer stem cells remain (116).

Besides selectivity, another consideration is how broadly can a therapeutic strategy be used. Though it is true that more aerobic glycolysis is widespread in most cancers (117), it has some significant exceptions and conditions when other metabolic programs outcompete aerobic glycolysis (118). Clinical trials underway are included in **Supplementary Table 3**. For the fourteen novel chemotherapeutic agents approved in 2024, ten are usable for less than 2% of cancers, based on target indication. Metabolic approaches, by comparison, may be applicable to a broader range of cancers, given the ubiquity of metabolic reprogramming in cancer cells (**Supplementary Table 4** and **Supplementary Figure 2**) (119). In practice, ketogenic diets may not be applicable to a most cancer cases, while most preclinical studies indicate an antitumor effect, 8% of preclinical studies of the ketogenic diet indicated a protumor effect (120).

TREATMENT USING METABOLIC APPROACHES

In the last ten years, there has been a surge of clinical research on metabolic therapies for cancer. Nevertheless, the general clinical evidence is still heterogeneous and is often limited by small sample sizes, inconsistent definitions of diets, divergence in adherence, and brief intervention periods. Although there are studies that document positive metabolic responses and indicators of clinical benefit in specific settings, oncology programs have not yet determined any consistent changes in tumor outcomes in various tumors, and encouraging results in a particular cancer type need to be validated in larger, sufficiently powered trials (121). Accounts of individual responses of remarkable difference among the patients following through with dietary regimes must therefore be viewed as hypothesis-generat-

ing as opposed to a conclusive indication of overall efficacy (122). Dietary interventions tend to be less expensive than most specific pharmacological treatments, and are commonly thought to have fewer acute toxic side effects, although this benefit must be balanced against unknown risks in the long term, and in active cancer therapy (123).

The metabolic interventions are usually characterized by high levels of carbohydrate restriction to achieve a ketosis condition, whereby the body starts to depend on ketones as the major energy source instead of glucose (124). Metabolic adaptation to ketosis occurs differently in different individuals depending on their initial dietary practices and clinical conditions. Fasting can also induce ketosis (125), and exogenous ketones, including beta-hydroxybutyrate, can also help hasten the process (126). Notably, achieving and maintaining therapeutic ketosis may be difficult in populations with oncology, specifically, during chemotherapy, radiotherapy, and periods of low intake.

At the early stage of adaptation, one could also have a lowered energy level, mainly because the glycolytic pathways are suppressed (127). This period of adaptation is not fixed, and occasionally, patients may drop the dietary regimen because of initial discomfort (128). Exogenous ketone use could help reduce the side effects of the initial phase, thereby promoting adherence (129). However, due to the nature of the majority of cancer trials, which evaluate ketogenic diets in rather short periods, the long-term metabolic, cardiovascular, renal, hepatic, and endocrine effects have not been well defined in cancer patients, and research gap for further research to close.

Given that 40-80% of cancer patients experience malnutrition (130), nutritional support should prioritize correction of documented deficiencies and maintenance of lean body mass under professional supervision (131). High-protein diets, albeit non-ketogenic, are effective at maintaining lean mass (132), while conflicting results show ketogenic diets alleviating (133) or worsening cachexia (134) in preclinical models. This variability in the clinical setting supports the necessity of close patient selection and monitoring, especially in patients with a loss of weight, frailty, sarcopenia, or oral intake restriction. In this context, the use of metabolism-directed supplements and repurposed drugs can be considered as supplements (135, 136).

Efficient decreasing of blood glucose is pertinent in the induction of ketosis and metabolic modulation techniques. It must be noted, though, that cancer metabolism is heterogeneous, and the therapeutic utility of glucose-lowering as an antitumor modality has not always been shown across different cancers in trials and has not been uniformly found useful in cancer therapy. Additionally, sustained carbohydrate restriction can pose certain risks, especially concerning oncology patients, such as the unknown long-term cardiovascular consequences and the lack of information regarding its renal, endocrine, and hepatic outcomes when used in the long term. Thus, any glucose-reducing plan must be introduced as investigational, preferably carried out under medical control and in a structured regimen (135). Drugs like berberine and re-purposed pharmaceutical metformin have shown effectiveness in decreasing blood glucose and enhancing glycemic control (137).

Repurposed drugs

Drug repurposing should be viewed within the context of drug development wherein 22% of drug development failures are due to drug toxicity (138), high attrition rates (>90%) hamper new drug development (139), with many failures happening in late stage preclinical or clinical testing, at a very high cost (140). In addition, the average antineoplastic agent takes 6.9 years to undergo clinical trials, and an extra 0.7 years for approval (141).

Given that the average cost of advancing drug to the market is ~$1.1 billion (142), early prediction of failure due to toxicity is vital. From 1990□2010, 133 drugs were pulled off the market due to safety reasons. The most notable examples were Vioxx from Merck & Co., Inc. (143) and Bextra from Pfizer Inc. (144) after cardiotoxicity was discovered (145). Furthermore, legal costs associated with Vioxx lawsuits reached almost $5 billion (146).

Identifying toxicity issues is an emerging market; the predictive toxicology market is growing at a compounded annual growth rate (CAGR) of 15% (2012) (147). This growth is based on the understanding that improved predictive toxicology tools may save millions of dollars in drug development costs (148). It should be noted that repurposed drugs largely obviate this issue of toxicity emerging later in development, as there is significant safety data available. Drug repurposing can be accelerated and optimized using computational prediction methods which are rapidly becoming highly reliable (149-152). This is typically followed by experimental and clinical validation of *in silico* data (153). Combinatorial chemistry

(154) and high throughput screening (HTS) quickly produce many therapeutic drug candidates, and *in silico* tools are becoming more accepted for rapidly selecting molecules for further development (155). The adoption of *in silico* methods allows for significant cost and time savings in both drug development and drug repurposing (156). The FDA has recently been discussing the development of computational toxicology platforms as part of safety assessment measures (157).

The advantages of drug repurposing are first, that it is an already available and known drug. As the estimated cost for new cancer drugs is on the order of hundreds of millions (often wrongly quoted as billions to justify exorbitant costs), significant cost savings can already be achieved by re-using already used drugs as opposed to bringing new drugs to market, which involves a long regulatory process and establishing manufacturing centers.

Repurposed drugs also have a known safety profile, which can aid in the cost-benefit analysis to use these drugs. While pre-licensing trials are performed for new cancer drugs, often they exhibit significant toxicity (158). While in many instances this tradeoff can be reasonable, still, a well-known side-effect profile is preferred. A safety signal takes a median duration 11.5 months to manifest and be detected after approval, and the median time to action following signal detection is another 21 months (159). Therefore, it takes almost 3 years for regulatory action to respond to a safety signal, in which time people continue to be harmed by the drug. Additional time also allows for tailoring of treatment, and 21% of evaluable new molecular entities (NMEs) approved between 1980 and 2000 had their dosages adjusted for safety (160).

Lastly, repurposed drugs are often generic and cheap drugs, lacking the patent protection extended to many NMEs (161). Generic drugs are almost universally cheaper than patented medicines (162, 163), and this can be a benefit to consumers. One counter-strategy by the industry is to develop 'me-too' drugs (164), which are almost identical molecular entities to a previously developed one, developed for the purpose of selling at patented medicine rates, which re higher than generic medications rates.

Overall, drug repurposing is a promising strategy not just for cancer, but for many diseases, especially emerging diseases where there is need for a swift response. Repurposed drugs, along with free informational sharing amongst practitioners, is a viable way to respond to future emerging health issues.

Important considerations

Using drugs in new contexts carries risks, though risk is in principle minimized through the existing safety record of the drug. The potential safety concerns associated with the use of repurposed medications, particularly when administered at higher doses or for new indications, are important to acknowledge. One of the primary advantages of repurposing established medications is the availability of an extensive safety record, often informed by both clinical studies and real-world use. In some cases, accidental overdoses have provided valuable insights into the safety margins of these drugs. For example, Chiew *et al.* describe a case in which a 55-year-old woman ingested 132 grams of extended-release metformin (165), far exceeding the typical therapeutic dose, and subsequently developed severe lactic acidosis.

While the established safety data for repurposed drugs can help mitigate some risks, the potential for unexpected toxicities remains, especially when novel drug combinations are employed. It is important to note, however, that this risk is generally lower than with entirely new chemical entities, as repurposed drugs benefit from a well-characterized safety profile, including known drug interactions and adverse effects at various dosages. Even clinical trials, which evaluate drugs in the intended patient population, may fail to detect certain safety signals if they are underpowered, do not assess relevant clinical outcomes, or if adverse effects are subtle or emerge only after prolonged exposure. These limitations can contribute to the identification of safety concerns only after a drug is approved and marketed. Notably, approximately 7% of approved drugs in the United States were withdrawn from the market due to safety issues between 1980 and 2009 (166).

For most repurposed drugs, the proposed dosages are within established ranges, allowing researchers to reference existing safety data for individual agents. However, the greatest risk of unforeseen adverse events arises from drug-drug interactions, particularly when novel combinations are used. While software tools exist to predict potential toxicities from drug-drug interactions, these approaches are not infallible (167). To mitigate these risks, a cautious, stepwise approach is recommended. This would involve initiating treatment with repurposed drugs at low doses, either as single agents or in combinations with well-established safety profiles, and gradually escalating

doses or introducing additional agents as appropriate. Such a strategy aims to minimize the likelihood of adverse side effects while maximizing patient safety.

INTEGRATIVE ONCOLOGY: THE FUTURE OF CANCER CARE?

The market for complementary and alternative medicine (CAM) comprised some 3% of total US healthcare spending in 2008 (168). Data from 2012 show US consumer expenditures on complementary healthcare approaches of $30.2 billion (169), compared to the $2.8 trillion in total healthcare spending that same year (170), or roughly 1%. One factor acting against CAM adoption is many expenses are not eligible for reimbursement by insurance providers (171), so more of the costs are borne out of pocket.

Despite comparatively low adoption in the US healthcare ecosystem, CAM is adopted widely in Asian countries (172), and integrative oncology enjoys institutional support in other countries (173, 174). US patients are open to integrative oncology, as evidenced by a majority of US cancer patients using some form of CAM during their treatment (175). CAM adoption in oncology appears largely patient driven, as an Australian survey showed a majority of cancer patients using some form of CAM, with 90% of respondents saying that doctors should consider learning more about CAM (176).

With regards to cancer treatment, CAM focuses on several areas: 1) prevention of initial cancer or recurrence, 2) use for an anticancer effect, typically alongside other treatments, or 3) to alleviate side effects of cancer or cancer treatment (177). Importantly, the National Cancer Institute has recommend against taking supplements, particularly antioxidant supplements, during cancer therapy (178), as these have been postulated to interfere with chemotherapy or radiotherapy (179). This guideline is supported by a recent study showing lower survival in individuals taking dietary antioxidant supplements compared to individuals not taking antioxidant supplements (180). Some natural products show preliminary evidence for their efficacy, but insufficient to make a recommendation.

However, despite the limited evidence for some modalities, practitioners may adopt unproven methodologies which may put patients at unnecessary risk, especially if they refuse conventional treatment (181, 182). While the use of unproven modalities carries definite harms, it should not prevent the adoption of evidence-based CAM. Currently, CAM is only recommended for addressing effects of cancer or cancer treatment, and not for treating cancer itself. Major cancer centers, such as MD Anderson and Memorial Sloan Kettering Cancer Center, have adopted interventions such as mindfulness, yoga and acupuncture (183), though these modalities focus on psychological symptoms.

A joint guideline document published in conjunction with the American Society of Clinical Oncology (ASCO) and the Society for Integrative Oncology (SIO) provides a strong recommendation for mindfulness based therapies as well as Qigong to alleviate fatigue during cancer treatment, and a conditional recommendation for American Ginseng (184). For anxiety and depression, the ASCO and SIO provide a strong recommendation for mindfulness based interventions, and moderate recommendations for yoga, hypnosis, and music therapy (184). For pain during cancer, manual therapies, including acupuncture, yoga, reflexology and massage received recommendations from the ASCO and SIO, along wide guided imagery with progressive muscle relaxation and hypnosis (185). A 2017 ASCO and SIO guideline on integrative oncology in breast cancer does not recommend or examine agents or modalities which would affect cancer recurrence or survival due to a lack of randomized control trial evaluating these endpoints (186). The focus of subsequent CIO guidelines for the use of adjunctive cancer agents has not included therapeutics focused on improving cancer recurrence or survival, as opposed to managing other symptoms (184).

Despite a lack of current evidence, several integrative therapies may improve cancer treatment through an anti-cancer effect (177), such as intravenous vitamin C (187) and mushroom extracts (188, 189), though the evidence does not rise to the level of clinical recommendation. While numerous agents, such as curcumin (190), show promise in *in vitro* experiments, these effects often do not translate to the clinic, due to bioavailability or differences in metabolism or effective concentration in both *in vitro* (191) and *in vivo* studies (192).

There is a cultural divide between patients interested in CAM and their doctors. Nearly half of US CAM users do not inform their doctors (193). Most physicians have a desire to increase their knowledge of CAM, though lack of education and the short time

spent with patients is a barrier to wider CAM adoption (194). Nurses are also more likely than doctors to be open to CAM (195, 196).

Interestingly, a survey in Pakistan showed greater skepticism towards the efficacy of CAM in the general student population than those students studying pharmacy (197). This finding, where those with more professional experience demonstrated greater openness to CAM, is echoed by a survey in Germany, which found that internists were more skeptical of CAM than family physicians with more experience (198). Still, recalcitrance on the part of conventional doctors and lack of understanding hampers CAM adoption (196, 199).

Considering these challenges to adoption, it is impendent upon advocates of integrative oncology to provide educational opportunities for conventional physicians, and to also demonstrate rigorously the benefits of integrative oncology. Communication between integrative oncologists and conventional physicians and oncologists will be the linchpin of wider adoption, and a compelling case can be made based on treatment efficacy, cost-efficacy, ease of treatment (able to perform in outpatient setting) and quality of life.

Industry strategies to influence the public presentation of science are well documented (200, 201). Cancer-center spending on advertising increased over 3-fold between 2005 ($54 million) and 2014 ($173 million) (202). Compared to the numerous oncology drugs available, only approved two botanical drugs are available on the market as of 2020 (203). Interest in CAM appears to be increasing (204), with popular books receiving accolades as well as wide readership (205-208). One downside of the popularization of CAM treatments is the greater level of non-professional advice circulating, which can be ameliorated by professional and accredited CAM consultation (209). Training CIM practitioners to be able to work with conventional oncologists is important for the success of the program (210).

Real-world examples

Israel has adopted integrative oncology at some of its cancer centers, and there are currently 10 active oncology complementary and integrative medicine (CIM) programs (173). The use of CAM in the urban Jewish population doubled from 6% in 1993 to 12% in 2007 (211). Beyond uptake, a study at the oncology service of the Lin Medical Center in Haifa Israel showed statistically significant increases in individuals' well-being, appetite, anxiety, depression, nausea and fatigue (212) when they participated in an integrative oncology program. Other studies have demonstrated decreased use of medications to manage cancer therapy side effects in an integrative oncology setting (213).

Beyond institutional integrative oncology, several practitioners used ketogenic diets in addition to standard of care (214). Increased awareness has improved the accessibility of metabolic treatments (215), even for those with dietary restrictions, such as vegans (216). While rigorous clinical trials are limited (217-219), clinicaltrials.gov lists 53 studies using ketogenic diets as an intervention for various types of cancers* (**Supplementary Table 2**) Recent meta-analyses have found that ketogenic diets in cancer may improve mental health (220), and while clinical data on treatment efficacy is limited, several published studies show improvements in survival rates (221-224), though expert meta-analysis evaluates the evidence for anti-cancer effects as weak to moderate (225). These trials are necessary to evaluate the efficacy and establish best practices for using ketogenic diets in cancer care, and should take place before recommendation as part of cancer care. Fortunately, active work is underway to rigorously assess ketogenic approaches to cancers (226).

FUTURE OUTLOOK

Trends in the incidences of specific cancers have been varying, and treatment remains a challenge for cancers. Currently, a paradigm shift is occurring in the metabolic understanding of cancer, which can potentially provide non-invasive interventions for prevention and treatment (both primary and adjuvant) of cancer. The metabolic paradigm in cancer treatment potentially allows for broad spectrum therapeutics against a common hallmark of cancer, a penchant for the fermentation of glucose in the presence of oxygen (97).

Combined with repurposed drugs, there is significant potential for a substantial decrease in the costs associated with cancer treatment (213), as well as improved treatment outcomes and quality of life (227).

Search terms "ketogenic diet" in "Interventions" and "cancer" in "Disease" fields. Search reveals 66 results, 14 results not relevant, either not cancer related or do not use a ketogenic diet. Final studies are shown in* ***Supplementary Table 1**.*

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Conflicts of interest

The authors declare no competing interests.

Availability of data and material

All data generated or analyzed during this study are included in this article.

Authors' contributions

MH: conceptualization, literature search, writing – original draft, visualization, writing – review & editing. PM: conceptualization, critical revision of the manuscript, supervision, writing – original draft, writing – review & editing. JV: writing – review & editing. JT: conceptualization, methodology, writing – review & editing, supervision, project administration.

Publications ethics

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. *Classes of food additives under European Union regulation.*

NO.	FUNCTIONAL CLASS	DEFINITION (1)
1	Sweeteners	Substances used to impart a sweet taste to foods or in table-top sweeteners
2	Colours	Substances which add or restore colour in a food, including natural constituents and preparations from foods obtained by physical/chemical extraction
3	Preservatives	Substances which prolong shelf-life by protecting against deterioration caused by micro-organisms and/or pathogenic micro-organism growth
4	Antioxidants	Substances which prolong shelf-life by protecting against oxidation (*e.g.*, fat rancidity, colour changes)
5	Carriers	Substances used to dissolve, dilute, disperse or physically modify additives, flavourings, enzymes, or nutrients without altering their function
6	Acids	Substances which increase acidity and/or impart a sour taste
7	Acidity regulators	Substances which alter or control the acidity or alkalinity of a foodstuff
8	Anti-caking agents	Substances which reduce the tendency of particles to adhere to one another
9	Anti-foaming agents	Substances which prevent or reduce foaming
10	Bulking agents	Substances which contribute to volume without contributing significantly to available energy value
11	Emulsifiers	Substances which form or maintain a homogenous mixture of immiscible phases (*e.g.*, oil and water)
12	Emulsifying salts	Substances which convert cheese proteins into dispersed form for homogenous fat distribution
13	Firming agents	Substances which maintain fruit/vegetable firmness or interact with gelling agents to produce/strengthen gels
14	Flavour enhancers	Substances which enhance existing taste and/or odour
15	Foaming agents	Substances which form a homogenous dispersion of gas in a liquid or solid foodstuff
16	Gelling agents	Substances which give texture through gel formation
17	Glazing agents	Substances which impart a shiny appearance or protective coating to external surfaces (includes lubricants)
18	Humectants	Substances which prevent drying out or promote powder dissolution in aqueous media
19	Modified starches	Substances from chemically treated edible starches (may include physical/ enzymatic treatment, acid/alkali thinning, or bleaching)
20	Packaging gases	Gases other than air introduced into a container before, during, or after placing a foodstuff
21	Propellants	Gases other than air which expel a foodstuff from a container
22	Raising agents	Substances which liberate gas to increase dough/batter volume
23	Sequestrants	Substances which form chemical complexes with metallic ions
24	Stabilisers	Substances which make it possible to maintain the physico-chemical state of a foodstuff; stabilisers include substances which enable the maintenance of a homogenous dispersion of two or more immiscible substances in a foodstuff, substances which stabilise, retain or intensify colour of a foodstuff and substances which increase the binding capacity of the food, including the formation of cross-links between proteins enabling the binding of food pieces into re-constituted food
25	Thickeners	Substances which increase the viscosity of a foodstuff
26	Flour treatment agents	Substances, other than emulsifiers, which are added to flour or dough to improve its baking quality
27	Contrast enhancers	Substances which, when applied to the external surface of fruit or vegetables following depigmentation of predefined parts (*e.g.*, by laser treatment), help to distinguish these parts from the remaining surface by imparting colour following interaction with certain components of the epidermis

Supplementary Table 2. *Environmental exposures associated with cancer risk, and the trend in exposure levels/rates.*

FACTOR	TREND	IMPACT ON CANCER IN ISOLATION	EXPOSURE LEVEL
Smoking	Global decrease of 28% for men and 38% for women between 1990 and 2019 (7)	RR = 46 for small cell lung cancer (SCLC) for male current smokers compared to men who have never smoked. RR = 22 for SCLC for female current smokers compared to women who have never smoked (8)	11.5% of US adults smoke (2021) (9)
Pesticide exposure-occupational	Increase in pesticide use 7% between 1996 and 2011(10)	Non-Hodgkin's Lymphoma associated with glyphosate exposure: RR = 1.3 (11) RR = 2.02 (12)	2.4 million farm workers in USA (2013) (13). 0.6% of USA farming acreage is organic*
Pesticide exposure -food	Glyphosate tonnage grew by 17% on average annually between 1990 and 2014 (16)	Organic food consumption associated with a decreased risk (RR = 0.79) of non-Hodgkin Lymphoma (17)	On average 1.0kg per hectare of farmland applied in USA (16) 59% of corn and soy samples test positive for glyphosate and glufosinate residues (18)
Beauty products	Global annual growth rate of 4.5% over the last 20 years (19) Decrease of 13% in North America from 1998 to 2007 (14)	Breast cancer hazard ratio 1.15 for frequent white female users of beauty products relative to infrequent users (15)	85% of adolescent girls use body products on a daily basis (16)
Fire retardants in furniture	Production of chlorinated organophosphate flame retardants increases from 14,000 tons per year (mid-1980's) to 38,000 tons per year (2012) (17)	Flame retardants decabromodiphenyl ether and tris(2-chloroethyl) phosphate associated with greater risk (RR = 2.3) of papillary thyroid cancer (18)	Ubiquitous in furniture owing to flame-retardant requirements of furniture (19), (20)
Radon exposure	Should be stable, Radon's source primarily geological (21)	Every 100 Bq/m^3 increase in Radon concentrated estimated to increase relative risk for lung cancer by 8-16% (22)	Second biggest cause of non-occupational lung cancer behind smoking (22)
Antibiotics	Drop in recent years in USA. 5% decrease in number of prescriptions between 2011 and 2016 (23). 25% drop between 2016 and 2020 (23), (24) Global increase from 9.8 defined daily doses (DDD) per 1000 per day in 2000 to 14.3 DDD per 1000 per day in 2018 (25).	RR = 1.37 between lowest and highest exposure group for cancer (26)	In USA, 613 antibiotic prescriptions per 1000 people in 2020 (24)
EMF exposure	Increasing (27)	Increased RR = 2.0 for childhood leukemia for exposures of ≥0.4 μT compared to <0.1 μT (28)	Ubiquitous
Sedentary lifestyle	Increase in 39% in rates of meeting physical activity guidelines between 1998 and 2013 (29) Declines in active transport among children and adolescents (30)	Combined healthy lifestyle reduced risk of cancer (RR = 0.29 compared to those reporting no physical exercise or positive health behaviors) (31)	2/3 of adults do not meet physical activity guidelines (150min per week of moderate to vigorous physical activity) (29)
Sleep deprivation	Relatively stable sleep duration in adults (32), (33), but decreases in sleep quality (34)	Increased risk of colorectal cancer (RR = 1.08) and lung cancer (RR = 1.11) in poor sleep category (35)	More than 1/3 of US adults sleep fewer than 7 hours per night (2014) (36)

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FACTOR	TREND	IMPACT ON CANCER IN ISOLATION	EXPOSURE LEVEL
Stress	Work stress has been on the rise in Europe (37)	Association between work stress and risk of colorectal (RR = 1.36), lung (RR = 1.24) and esophageal (RR = 2.12) cancers (38)	71% of employees typically feel tense or stressed out during the workday (2019) (39)
Caesarean birth	Increase in rate of caesarean section from 30% in 2003 to 37% in 2010(40)	Increased rate of childhood kidney cancer (RR = 1.25) (41)	Approximately one-third of North American births in 2010 (42)
Family size	Decrease from 3.33 in 1960 to 2.50 in 2022 (43)	Hodgkin's Lymphoma risk lower for increased number of older siblings: RR = 0.72 for three or more older siblings compared to none (44) RR = 0.41 for five or more older siblings compared to none (45) Acute monocytic leukemia RR = 0.35 for three or more older siblings compared to none (45) Acute lymphoblastic leukemia RR = 0.69 for three or more older siblings compared to none (45)	Average family size of 2.50 in 2022 (43)
Mother's age at first birth	Increasing (46)	RR~1/3 for women giving birth before age 18 compared to those giving birth after 35 (47)	Average age in USA is 27.1 years (2020) (48)
Febrile illness	No trend in presentation rates to emergency department (49)	Lower rates on non-breast cancers for adults experiencing childhood febrile illness (50)	2.8 million children <2 years with fever present to emergency departments annually in USA (49)
Hormonal birth control	In the UK, hormonal birth control prescription proportion dropped 45% between 2000 and 2018 (51). Between 1995 and 2010, approximately 82% of sexually experienced women use the pill, staying relatively constant (52)	RR = 1.20 for breast cancer for users compared to non-users (53)	one in four US women aged 15-44 using oral contraceptives (2013) (54)
Breastfeeding (mother)	Increase in proportion of mothers breastfeeding from 75% in 2010(55) to 81.1% in 2016 (56)	Decrease in 2% breast cancer risk for every 5 months breastfeeding (57). Decreased risk of premenopausal breast cancer (RR = 0.88) (58) RR = 0.76 for invasive epithelial ovarian cancer (59)	81.1% of mothers breastfeed at birth (2016) (56)

**Total certified organic acres operated 5.5 million (2019) (14). Total land in farms 897.4 million acres (2019) (15).*

Supplementary Table 3. *Clinical trials for ketogenic diets in the treatment of cancer.*

NCT NUMBER	STUDY TITLE
NCT06896552	Single-Center Trial on Ketogenic Diet and Immunotherapy in Advanced Cancer This Study Evaluates the Safety and Effects of a Ketogenic Diet (KD) Combined With Immunotherapy in Adults With Advanced Melanoma, cSCC, or RCC
NCT06391099	Ketogenic Dietary Intervention to Improve Response to Immunotherapy in Patients With Metastatic Melanoma and Metastatic Kidney Cancer
NCT06106139	Ketogenic Diet Improves Thrombocytopenia in Cancer Patients
NCT06046755	Nutritional Intervention-induced Weight Loss During the Oncological Treatment of Obesity-related Breast Cancer
NCT05938322	Ketogenic Diet Compliance in Patients Affected by Locally Advanced Rectal Cancer Patients Who Undergo to Radiotherapy
NCT05708716	Diet and Cognitive Training in Hematologic Cancer Survivors
NCT05708352	A Phase 2 Study of the Ketogenic Diet *vs* Standard Anti-cancer Diet Guidance for Patients With Glioblastoma in Combination With Standard-of-care Treatment
NCT05564949	A Ketogenic Diet as a Complementary Treatment on Patients With High-grade Gliomas and Brain Metastases
NCT05428852	Keto-Brain:Investigating the Use of Ketogenic Diets in Brain Metastases
NCT05373381	The KetoGlioma (Ketogenic Glioma) Study
NCT05234502	Effects of Ketogenic Diet in Overweight and Obese Women With Breast Cancer
NCT05183204	Paxalisib With a High Fat, Low Carb Diet and Metformin for Glioblastoma
NCT05119010	A Pilot Study Evaluating a Ketogenic Diet Concomitant to Nivolumab and Ipilimumab in Patients With Metastatic Renal Cell Carcinoma
NCT05090358	Preventing High Blood Sugar in People Being Treated for Metastatic Breast Cancer
NCT04750941	Study of Copanlisib and Ketogenic Diet
NCT04730869	Metabolic Therapy Program In Conjunction With Standard Treatment For Glioblastoma
NCT04691960	A Pilot Study of Ketogenic Diet and Metformin in Glioblastoma: Feasibility and Metabolic Imaging
NCT04631445	Study Evaluating the Ketogenic Diet in Patients With Metastatic Pancreatic Cancer
NCT04469296	Diet Modification in pAtients With Luminal Early Breast Cancer Candidate for Primary Surgery
NCT04461938	Characterization of Metabolic Changes in the Glioma Tumor Tissue Induced by Transient Fasting (ERGO3)
NCT04316520	Ketogenic Diet for Patients Receiving Treatment for Metastatic Renal Cell Carcinoma
NCT04231734	Ketogenic Diet in Patients With Untreated Low Tumor Burden Mantle Cell Lymphoma
NCT03962647	A 2-Week Ketogenic Diet in Combination With Letrozole to Modulate PI3K Signaling in ER+ Breast Cancer
NCT03955068	Strict Classic Ketogenic Diet as a Therapy for Recurrent or Progressive and Refractory Brain Tumors in Children
NCT03679260	Carbohydrate Restricted Diet Intervention for Men on Prostate Cancer Active Surveillance
NCT03591861	Therapeutic Targeting of Sex Differences in Pediatric Brain Tumor Glycolysis
NCT03535701	Ketogenic Diet and Chemotherapy in Affecting Recurrence in Patients With Stage IV Breast Cancer
NCT03451799	Ketogenic Diet in Combination With Standard-of-care Radiation and Temozolomide for Patients With Glioblastoma
NCT03328858	Ketogenic Diet in Children With Malignant or Recurrent/Refractory Brain Tumor
NCT03285152	A Study of Ketogenic Diet in Newly Diagnosed Overweight or Obese Endometrial Cancer Patients
NCT03278249	Feasibility Study of Modified Atkins Ketogenic Diet in the Treatment of Newly Diagnosed Malignant Glioma
NCT03194516	Ketogenic Diet and Prostate Cancer Surveillance Pilot
NCT03171506	Targeted Disruption to Cancer Metabolism and Growth Through Dietary Macronutrient Modification
NCT03160599	Restricted Calorie Ketogenic Diet as a Treatment in Malignant Tumors
NCT03075514	Ketogenic Diets as an Adjuvant Therapy in Glioblastoma
NCT02983942	Ketogenic Diet Adjunctive to HD-MTX Chemotherapy for Primary Central Nervous System Lymphoma

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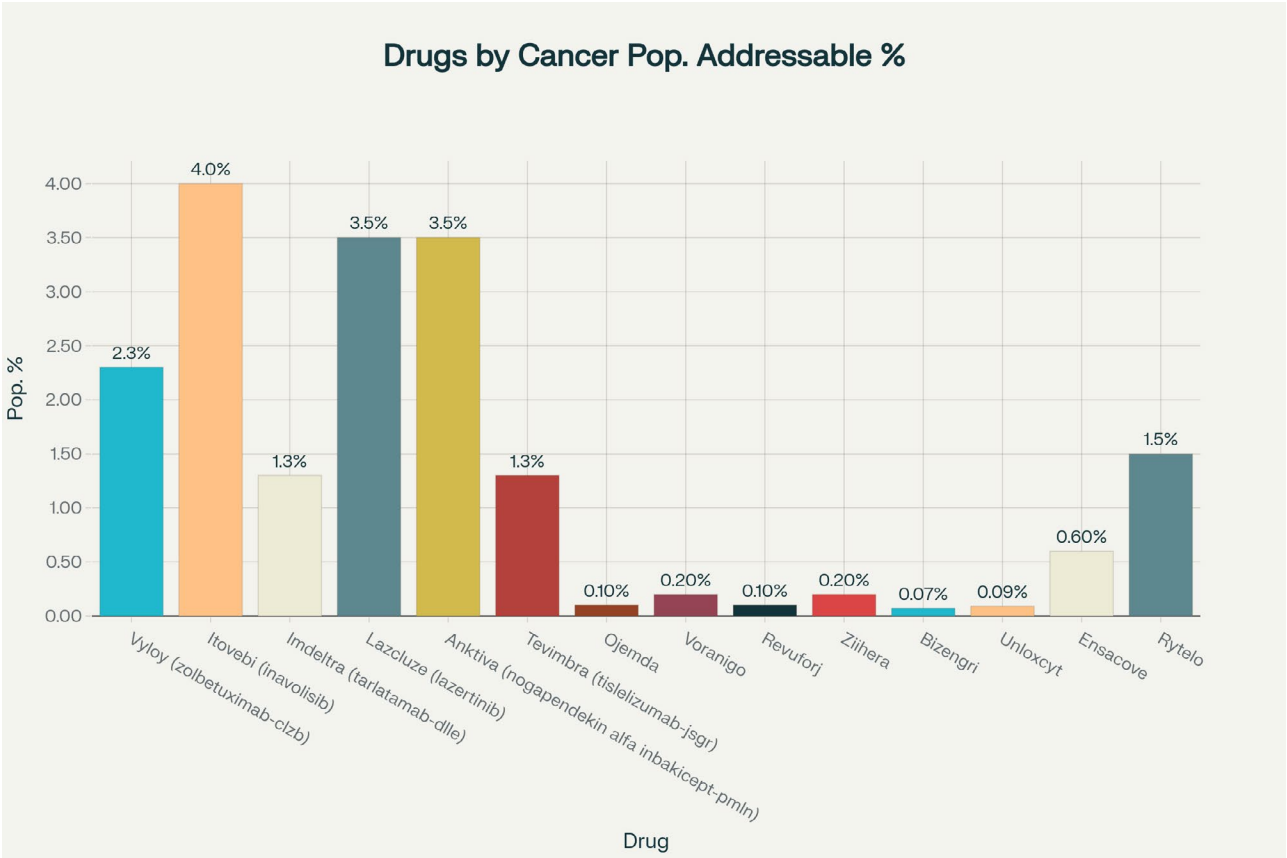
NCT NUMBER	STUDY TITLE
NCT02964806	Development and Clinical Validation of Ketogen-based Therapeutic Diet for Pancreaticobiliary Cancer Patients
NCT02939378	Ketogenic Diet Adjunctive to Salvage Chemotherapy for Recurrent Glioblastoma:a Pilot Study
NCT02516501	Impact of a Ketogenic Diet Intervention During Radiotherapy on Body Composition
NCT02302235	Ketogenic Diet Treatment Adjunctive to Radiation and Chemotherapy in Glioblastoma Multiforme: a Pilot Study
NCT02286167	Glioma Modified Atkins-based Diet in Patients With Glioblastoma
NCT02092753	Ketogenic Or LOGI Diet In a Breast Cancer Rehabilitation Intervention (KOLIBRI)
NCT02046187	Ketogenic Diet With Radiation and Chemotherapy for Newly Diagnosed Glioblastoma
NCT01975766	Ketogenic Diet Phase 1 for Head & Neck Cancer
NCT01865162	Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study
NCT01754350	Calorie-restricted, Ketogenic Diet and Transient Fasting During Reirradiation for Patients With Recurrent Glioblastoma
NCT01716468	Ketogenic Diet in Advanced Cancer
NCT01535911	Pilot Study of a Metabolic Nutritional Therapy for the Management of Primary Brain Tumors
NCT01419587	Ketogenic Diet With Chemoradiation for Lung Cancer (KETOLUNG)
NCT01419483	Ketogenic Diet With Concurrent Chemoradiation for Pancreatic Cancer
NCT01092247	The Effect of Ketogenic Diet on Malignant Tumors- Recurrence and Progress
NCT00575146	Ketogenic Diet for Recurrent Glioblastoma



Supplementary Figure 2. *Drugs by cancer population.*

Supplementary Table 4. *Addressable population for new anticancer agents approved in 2024. For new anticancer agents approved in 2024 (60), based on their indication, the addressable population as a percentage of cancer patients is calculated.*

TREATMENT (GENERIC NAME)	INDICATION	ADDRESSABLE POPULATION (% OF CANCER CASES)
Lumisight (pegulicianine)	Imaging agent for detection in breast cancer	N/A
Vyloy (zolbetuximab-clzb)	Gastric, gastroesophageal junction cancers (CLDN18.2+)	~6% of cancers are gastric cancers (61) 38% of those with gastric cancers are claudin (CLDN18.2) positive (62) Vyloy is applicable to ~2.3% of cancers
Itovebi (inavolisib)	HR+, HER2-, PIK3CA-mutated advanced/ metastatic breast cancer	Breast cancer is ~15% of total cancers (63) HR+/HER2- are ~70% of female breast cancer (64) PIK3CA mutation in ~40% of HR+ breast cancers (65) Itovebi is applicable for ~4% of cancers
Imdeltra (tarlatamab-dlle)	Extensive-stage small cell lung cancer	Lung cancer is ~11% of cancers (66) SCLC ~15% of lung cancers (67) ES-SCLC is 2/3 of SCLC cases (68) Imdeltra is applicable for ~1.3% of cancers
Lazcluze (lazertinib)	EGFR-mut. non-small cell lung cancer	11% of cancers are lung cancer (66) ~85% of lung cancers are NSCLC (69) 32.3% of all NSCLC cases are EGFR-mutated (70) Lazcluze is applicable to 3.5% of cancers
Anktiva (nogapendekin alfa inbakicept-pmln)	BCG-unresponsive non–muscle-invasive bladder cancer	Lung cancer ~13% of all cancers NSCLS ~85% of lung cancers (67) EGFR mutations in 32% of NSCLC patients (70) Anktiva is applicable to 3.5% of total cancers
Tevimbra (tislelizumab-jsgr)	Esophageal Squamous Cell Carcinoma (ESCC) Gastric or Gastroesophageal Junction Adenocarcinoma (G/GEJ)	Gastric cancers ~1.5% of total cancer cases in the USA (71) GEJ cancers are 33% of all gastric cancers (72) Esophageal cancers are 1% of cancers in the USA (71) ECSC are 80% of all esophageal cancers (73) Tevimbra is applicable for ~1.3% of all cancers
Ojemda	Pediatric low-grade glioma	Childhood cancers ~1–2% of all cancers (WHO) (74). Brain & CNS tumors ~20–25% of childhood cancers (ACS) (75). pLGG is 33% of pediatric brain tumors (ABTA) (76). Ojemda applies to ~0.1% of cancers.
Voranigo	IDH-mutant glioma (astrocytoma/ oligodendroglioma)	Brain & CNS tumors 1.6% of cancers (77). ~70–90% of Grade 2 gliomas are IDH mutant (78), (79). Voranigo applies to ~0.2% of cancers.
Revuforj	Acute leukemia with KMT2A translocation	Leukemias account for ~2–3% of cancers (80). ~50–55% are acute leukemias (81). ~10% KMT2A rearrangements (82). Revuforj applies to ~0.1% of cancers.
Ziihera	HER2-positive biliary tract cancer	BTC ~1% of cancers (83, 84). ~5–20% HER2-positive cases (85). Ziihera applies to ~0.2% of cancers.
Bizengri	NSCLC and pancreatic adenocarcinoma with NRG1 fusion	Lung 12.4% (77). Pancreas 2.6% of cancers (77). NRG1 fusions <1% in these (86), (87). Bizengri applies to ~0.07% of cancers.
Unloxcyt	Cutaneous squamous cell carcinoma	Together, skin cancers (MSC + NMSC) make up ~8% of all global cancers (83), (88). CSCC constitutes 20-50-% of all skin cancers (89), (90). 1–4% progress to advanced/metastatic (91). Unloxcyt applies to ~ 0.02–0.16% of cancers.
Ensacove	ALK-positive NSCLC	Lung cancers account for 12.4 % of all cancers (77). ALK rearrangement occurs in 5-6% of NSCLC (92). Ensacove applies to ~0.6% of cancers.
Rytelo	Myelodysplastic syndromes	MDS1–2% of all cancers (93). Rytelo applies to 1-2% of cancers.

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