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RESEARCH ARTICLE

Back to the Future – A 19th Century Perspective on Cancer

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ABSTRACT.
Several lines of evidence suggest that current negative trends in cancer incidence represent a deteriorating exposome. Analysis of its key components may enable focused and specific cancer prevention strategies beyond the scope of current diet and lifestyle recommendations, and may also be helpful for the increasing numbers of patients in remission. An outline chemo-preventive strategy is derived from historical data and developed for modern use.

Keywords: cancer, survival, anastasis, resistance, prevention, diet, mid-Victorian

Introduction:

In this article Dr. Paul Clayton tackles one of the most critical medical problems of our time; the rising incidence of cancer and the impact of diet and lifestyle on its prevalence and incurability. He notes that today's adulterated diet and sedentary lifestyle direct the biological milieu of our bodies towards a pro-inflammatory and immune suppressive posture, creating a pro-carcinogenic environment, and reviews the weakness of current strategies.

While chemotherapeutics can deliver an antitumor response, they generally eventually fail due to disease resistance and relapses; with resistance being a mechanism adapted by the cancer cell through modulation of alternate intrinsic survival pathways and relapse a testimony to compromised immune surveillance. He links these phenomena with the well-known issues of carcinogenesis promoting diets and progressively deteriorating lifestyles, and makes intriguing comparisons to the very different populace and public health of the mid-Victorian era of England.

While he may be accurate in his assumptions, the comparison is empirical and scientifically difficult to establish. What is commendable is his simplified proposal, founded on a historical and a mechanistic perspective, that invites food and other industries to collectively design pre-emptive and chemo-protective products and strategies designed to support immune surveillance and reduce exposure to oncogenic factors. His affirmative message is one of cancer prevention through diet and lifestyle modification – a path both validated and disintermediating.

To achieve really substantial gains, legislative and societal change may eventually be required.

Text:

After half a century of extensive research, and vast numbers of clinical trials - ClinicalTrials.gov currently lists 433,955 studies[1] - cancer remains the second-leading cause of death in the United States after heart disease. It is first or second cause in all developed countries and it's getting worse; over the last few decades, the incidence of cancer in adults under 50 years of age has steadily increased in those countries[2]. We currently experience a 50% and rising lifetime risk[3, 4], with the incidence of many cancers increasing with every generation[2].

It is not just a matter of a single cancer, which might possibly be attributed to a specific stressor. This is a very general problem, involving cancers of the breast, colorectum, endometrium, esophagus, extrahepatic bile duct, gallbladder, head and neck, kidney, liver, bone marrow, pancreas, prostate, stomach and thyroid[2]. (Cervical cancer, which is significantly prevented by the HPV vaccine, is a notable exception).

The fact that these cancers are increasing in younger adults indicates that causative factors are in play from an early age. The trend also implies that our many defenses against cancer, which we share with most multi-cellular organisms, are being progressively eroded. Diet and lifestyle factors are clearly involved, but public health operates in a political and an economic context and prevention lags far behind cancer treatments.

This is unfortunate.

Limitations of Treatment

Despite significant and ongoing advances in cancer survival and treatment success rates, chemotherapeutic drugs generally reach a point of failure. In a significant number of cases they fail in the short to medium term, because the patient dies with overwhelming infection enabled by immunosuppression or from some acute iatrogenic effect. Generally, however, this approach fails in the longer term because it induces resistance. Initially positive results are generally followed by resurgence, and very often increased malignancy[5-8]. Currently, 90% of chemotherapy failure is due to the growth and metastasis of cancers related to drug resistance[8, 9].

Solid cancers contain many different types of cancer cells, which function in a coordinated and collective manner. In this sense a tumor is very like an organ, or perhaps even an organism. These different cells are genetically diverse with differing functions, genomes and epigenomes, and hence different susceptibilities[9-11]. Due to this genetic diversity some cancer cells are better able to avoid, sequester, metabolize or excrete drugs, have enhanced repair/increased tolerance to DNA damage or higher antiapoptotic potential.

The cancer collective responds and attempts to adapt to its microenvironment[9, 10], as all living entities do. Apply chemo, and standard Darwinian rules apply. Vulnerable cells die, cells more able to withstand the drug survive and the cancer mass eventually becomes drug-resistant.

This is like antibiotic resistance, but worse. When treating infection, antibiotics do not kill all the pathogenic bacteria but reduce their numbers to the point where the immune system can take over. The

various tools used to treat cancer degrade immune function and makes it less able to complete the process, so now the balance of power shifts further to the cancer.

A recent review put it like this: 'A brief review of the history of cancer research makes one wonder if modern strategies for treating patients with solid tumors may sometimes cause more harm than benefit'[11].

And it gets more complicated.

In common with all life forms, cancer is driven to survive by a sort of imperative to live, an impulse to grow, continue and breed. This not only occurs at the cellular level, but also at the level of the whole cancer. There is a bewildering interplay of information within the cancer, with multiple mediators exchanging information between different populations of cancer cells and between cancer cells and host cells including connective and immune cells[8-11].

If (when) treatment doesn't kill all cancer cells outright but leaves a few at the verge of death, some of those cells may coopt intracellular machinery normally involved in physiological healing, and rebound into life. This is termed anastasis, Greek for 'rising to life'[12-22]. Those cells that do come back are more invasive than before[12], and they drive other cancer cells towards compensatory proliferation[18, 19]. They do so via activation of Caspase-3, a protein normally linked to apoptosis in damaged cells but which can take on an opposite role[17-18], promoting carcinogenesis, metastasis and therapy resistance.

These proliferation-stimulating and pro-survival pathways have been referred to as 'Phoenix Rising'[16, 19-22], with cancer rising from the ashes of the tumor that was targeted by chemo or radiotherapy. The cancer emerges more 'determined' than ever to succeed. This is an important cause of treatment failure.

Next generation immune-modulatory therapies undoubtedly present with improved therapeutic indices.

Tigilanol tiglate, a small molecule isolated from the seed of the Australian plant Fontainea picrosperma, is generating positive results in animal cancer[23]. Injected directly into tumors, it promotes a localized immune response which frequently results in complete remission. It has recently been synthesized[24], and is currently undergoing clinical trials[25]. Generalised immune responses stimulated by various cancer vaccines also look very promising, and Flt3L-NDV combinations and other variants are generating extremely positive results[ie 26, 27].

If they can be made available within reasonable pricing systems the vaccines, tigilanol tiglate and its analogues will likely change the treatment landscape. However, it will be some time before they are available for general use.

All the above makes cancer prevention an attractive option. If we could optimize it and standardize it, we could theoretically reduce the numbers of those who are diagnosed with cancer and subsequently require treatment. If, perhaps, we could learn the lessons of the past.

19th Century Experience Of Cancer

In mid-Victorian England (1850-1900) cancer was recorded as a relatively minor cause of death, in a population with an average life expectancy (after age 5) comparable to today's social classes C and D, which most closely resemble the mid-Victorian population[28]. This is reasonably similar to the situation that prevails in contemporary vestigial groups[ie 29]. Among the Bolivian Tsimane endometrial, ovarian, breast, prostate, lung and colorectal cancers appear to be rare; although cancers with a more infectious etiology, such as cervical cancer, are more common[30].

It is worth reviewing those factors which might have protected our ancestors, and now appear to be leaving us vulnerable. The Victorian exposome was very different to ours, as represented in the following, far from comprehensive table[28]:

Table 1: A comparison of 19th and 21st century exposomes

	Mid-Victorians	Today
Obesity	Rare	Prevalent
Adipokines	Neutral	Pro-inflammatory
MetS / NIDDM	Rare	Prevalent
q6/q3	2-3:1	15-25:1
Colonic microbiota b-glucuronidase / LPS	Eubiosis - / -	Dysbiosis + / +
Phytonutrients: apoptosis, re-differentiation, ECM	10-15g/day	0.5-1.0 g/day
Phase 2 inducers	+ + + +	+
1-3, 1-6 b glucans	+ + + +	+
Cooked meat carcinogens	+	+ + + +
Tobacco, spirits	+	+ + + +
AMP-K / MTORC1	**ON** / off	off/ **ON**

Estrobolome (totality of bacteria in the gut capable of metabolising and modulating circulating estrogen), LPS (lipopolysaccharides derived from gram -ve colonic microbiota), Phase 2 inducers (typically polyphenols),1-3, 1-6 beta glucans (yeast-fermented foods and contaminants), cooked meat carcinogens (produced in high temperature processes such as grilling and barbequing), AMP-K (AMP-activated protein kinase), MTORC1 (mammalian target of rapamycin complex 1) MetS (metabolic syndrome), ECM (extracellular matrix stabilisation).

Cancer cells were likely being formed in the bodies of mid-Victorians at the same rate as today, but were emerging in a well-defended environment. The cancer statistics of the period[31], while imperfect, suggest that that relatively few of those cancers achieved clinical significance.

The mid-Victorian diet consisted almost exclusively of basic produce with low calorific / high phytonutrient density[28], and contained none of the ultra-processed foods which dominate today's diet, and are increasingly linked to cancer[32-34]. Their cooking techniques were generally low temperature ie below 100C, spirits were rarely consumed and tobacco seldom smoked, although taken as snuff[28]. In an age before IT and the internal combustion engine, men and women were considerably more physically active than we are today[28]. Type 2 Diabetes, a leading cause of cancer deaths today[35], was rare[36], as was obesity.

Due to the mid-Victorian exposome, the mid-Victorian milieu interieur was anti-inflammatory, euglycemic and eubiotic. It was more immune-competent than ours, with b-glucan mediated up-regulated innate immunity[37-39] and an enhanced TH1/TH2 Ratio[40]. It was replete with polyphenols, carotenoids and a range of other phytonutrients which inter alia promote cancer cell re-differentiation, cell-cycle arrest, apoptosis and ferroptosis, cell contact inhibition, enhanced innate immune functions and ECM stabilisation[41-50]. Cancer cells emerging in this terrain were confronted with multiple barriers to survival and growth.

In marked contrast the modern milieu tends to be pro-inflammatory, immune-compromised, hyper-glycemic, dysbiotic and depleted in chemo-preventive phytonutrients. It is exposed to higher intakes of cooked meat and similar carcinogens, and the industrial diet's reduced content of phase 2-inducing phytochemicals likely extends their half-

life in the body. Our lower intakes of prebiotic fiber create an unhealthier colonic microbiota[51], with shifts in estrogen and estrogen metabolites linked to an increased risk of breast cancer[52, 53]. Prostate cancer risk may also be affected, although the data are diverse. Our lower levels of physical activity lead inter alia to increased mTOR signalling[54].

Current public health trends indicate that the above factors create a cancer-friendly environment.

It will be objected that many phytonutrients have been tried as single agents in cancer models, and found wanting. This is entirely unsurprising, and is more of a reflection of today's mono-therapeutic / pharmaceutical mind-set than of the way in which a pre-transitional diet and lifestyle operate to provide very many obstacles to cancer progression. This resembles antimicrobial or chemotherapeutic polypharmacy, where multiple agents are co-administered to make it more difficult for the target to acquire resistance.

This cancer-hobbling is hinted at in mid-Victorian cancer statistics[31, 55].

Daniel McLachlan was Principal Medical Officer of the Royal Chelsea Hospital in London between 1840 and 1863, with ongoing responsibility for over 500 patients. His magnum opus 'A Practical Treatise on the Diseases and Infirmities of Advanced Life', published in 1863, was a leading geriatric medicine textbook of the time. In 800 pages of detailed clinical observations, he makes only a few references to cancer (primarily of the GI tract), and describes a series of 854 death records which included only 47 cases of cancer[55].

At a 5.5% incidence, mid-Victorian overall cancer rates were approximately 10% of ours, if McLachlan's figures are accurate. Given the technology of the time, how much weight can we put on them?

While he and his colleagues' ability to detect cancer at an early stage was considerably less advanced than our own, the data noted here are based on autopsies conducted by physicians who recorded cancer without prejudice, and who were certainly able to identify gross tumors post mortem. The leukemias, too, were already well characterised by that time[56].

The mid-Victorian autopsy data may therefore reflect, however imperfectly, the 10% of cancer subjects in whom a genetic risk factor can be identified. McLachlan alludes to this, noting a strong familial disposition to ie stomach cancer[55]. He could see a link that is today largely obscured by the larger numbers of cancers occurring in individuals without genetic risk, but subject to a cancer-promoting exosome.

There is another apparent key point of difference between ourselves and the mid-Victorians.

We expect the incidence of cancer to rise exponentially with age, in line with the Ames model of accumulating gene mutations over time. This pattern may in fact be an artefact, due to the extensive disrepair of our multiple cancer defenses. Cancer cells arriving at any age are likely to survive and, over time, present as clinical disease. Given a similar number of cancer cells being added to the total per unit of time, the rate of clinical emergence will undoubtedly increase as we age and our immune systems decline.

In a mid-Victorian, cancer cells emerging at any age were subject to multiple barriers to progress, and generally failed to thrive. Among the mid-Victorians this reportedly produced a different temporal frequency of clinical cancers, with an average age of presentation of circa 40[57-59], compared to 60 today. This suggests that a significant number of these cases may have been genetically susceptible ones, as suggested above; and if this is indeed the case, it would then follow that mid-Victorians without genetic risk factors were substantially less at risk than their counterparts today.

Finally, and for comparative purposes, it is interesting to consider cancer rates in other animals. Among 42 species of primates kept in controlled and optimised conditions (ie without predation and with minimal risk of trauma), the cancer mortality rate is circa 5%[60]. This more closely resembles vestigial and reported mid-Victorian rates than our own, and appears to make contemporary Homo sapiens an outlier.

Strategic Prevention

A strategy to reduce exposure to carcinogenic factors, up-regulate all of our many anti-cancer defenses and perhaps restore or at least move towards mid-Victorian rates of cancer, starts with abstention from tobacco and alcoholic spirits, and avoidance or at least minimisation of ultra-processed foods. The second step adds weight maintenance and exercising for at least 15 minutes a week[61].

A third step may eventually involve nutritional enhancement via functional foods and supplements designed specifically to recreate a pre-transitional

metabolome. This could be achieved by combining an omega-3 HUFA/amphiphile polyphenol combination, a blend of prebiotics with different fermentation rates, and a comprehensive micro- and phytonutrient support program designed to reproduce the mid-Victorian profile.

This strategy may not only help reduce the numbers of patients requiring cancer treatment, but also provide support to those who have been treated and are now in remission, a group for which we currently have no substantive recommendations. Its efficacy will theoretically be measurable via pending blood pre-cancer blood tests Galleri, PanSeer, CancerSEEk et al, and eventually by clinical cancer rates.

The entrée to such a program depends on the food industry developing healthier products than the foods they currently sell, whether voluntarily or subsequent to legislation. We might then have a chance to set a global preventive program in place, and raise our public health from the ashes where it currently languishes.

Conclusion

It is generally accepted that cancer incidence is increasing, and that the modern exposome (diet and lifestyle) is driving this. Reducing as many cancer-friendly components of the exposome as can be identified, and as informed by historical data, should help to reduce today's cancer burden. This may be achieved via a new generation of functional foods and/or via targeted supplementation.

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McLachlan: If we look around, we behold on every side men and women of seventy, eighty, nay, ninety and upwards, still hale and hearty, without any indications of approaching dissolution. These are exceptional but their number is increasing from year to year, not only relatively but absolutely. …. Under normal circumstances, natural decay sets in between 50 and 55, though it is often deferred to a later period …

Louis XV1 director general of finances, Jaques Necker: 'The era of threescore and ten is an agreeable age for writing; your mind has not lost its vigour, and envy leaves you in peace'.