hypothesis

Title:
Cancer Prevention and Treatment with Immune System Boosting Interventions

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Abstract:
Cancer risk is known to increase tremendously when the immune system is suppressed, e.g., as observed in young organ-transplant recipients and AIDS patients. Based on such data, it may be hypothesized that the main reason for the development of clinical cancer is the weakening or suppression of the immune system, and that uncontrolled multiplication of cancer cells occurs when some aspects of the immune system fall below certain critical levels. Therefore, cancer may be prevented and treated by boosting these critical aspects of the immune system so that they are maintained above the critical levels. If multiple immune system boosting interventions are utilized, many aspects of the immune system would be boosted, increasing the likelihood of enhancing the critical aspects of the immune system and generating a cancer preventive and/or therapeutic effect. Clinical trials are needed to validate this approach for cancer prevention and treatment. If validated, the proposed approach could result in a major reduction of the death and suffering caused by cancer in the world.

Background
The war on cancer has been fought during the past several decades primarily based on the somatic mutation model of cancer(Tomasetti et al. 2017). Even though many advances have taken place in the cancer field(Heymach et al. 2018), there are indications that we are far from winning the war on cancer(Leaf 2014). Age-adjusted cancer mortality rate in the USA continues to be high(Xu et al. 2018) and cancer has become the leading cause of death in high income countries overtaking heart disease(Dagenais et al. 2019). The cancer drugs that have been approved for use in the recent years, while they are very expensive, have led to a median gain of only 2.1 months in the overall survival of cancer patients(Fojo et al. 2014). The adverse side effects of the cancer treatments are affecting the quality of life(Langbaum et al. 2019) for the increasing number of cancer survivors(Bluethmann et al. 2016), who, in addition, face substantial financial toxicities due to the high costs of the treatments(Gordon et al. 2017). Though there has been a small and steady reduction of cancer mortality rate in the USA since the early 1990s(Xu, Murphy et al. 2018), much

of the decrease may be attributed to the reduction in smoking that began in the 1960s(Thun et al. 2006), implying that the reported advances in the cancer field in the recent years have not led to a large reduction in the mortality of cancer patients. It is clear that a better approach is needed to reduce the death and suffering caused by cancer. In this article, I discuss an approach based on the immune suppression model of cancer(Doss 2016).

Immune suppression model of cancer

Cancer risk is known to increase by a factor of 40 or more in immune-suppressed young individuals, e.g., young patients with AIDS(Biggar et al. 2000) and young organ-transplant recipients(Acuna et al. 2016). Such a large increase in the cancer risk when the immune system is suppressed indicates that the immune system plays a major role in preventing the development of clinical cancer. Therefore, when cancer cells are formed with the accumulation of mutations, the immune system may eliminate them or keep them under control, resulting in covert cancers(Koebel et al. 2007), which almost everyone has(Greaves 2014). If the immune system becomes weak or is suppressed, e.g., due to aging, the covert cancers would be able to grow uncontrollably causing clinical cancers. I am referring to this concept for the development of cancer as the immune suppression model of cancer(Doss 2016). In a prospective study of adults aged 40 and over(Imai et al. 2000), those with low cytotoxicity of peripheral-blood lymphocytes were found to have higher cancer incidence rates during the subsequent years when compared to those with high cytotoxicity, supporting the immune suppression model of cancer. There is a considerable amount of additional evidence for this model of cancer, in the form of increased cancer risk when the immune system is suppressed and vice versa(Doss 2019).

Prevention and treatment of cancer

Let us now discuss how we can approach cancer prevention and treatment based on the immune suppression model of cancer. Many aspects of the immune system are known to decline with age(Lewis et al. 1978, Hazeldine et al. 2012, Kubota et al. 1991), reducing its ability to eliminate the cancer cells as we age. In particular, if some aspects of the immune system fall below certain critical levels, cancer cells would be able to grow without control. Let us assume that cancer cells begin to multiply uncontrollably in an individual at the time $t=t_0$ and that the multiplying cancer cells would develop into a malignant tumor. At the time $t=t_0-\Delta t$, where Δt is some finite time interval, the cancer cells were not multiplying uncontrollably. According to the immune suppression model of cancer, the reason that the cancer cells began to multiply uncontrollably at the time $t=t_0$ is that some aspects of the immune system declined below certain critical levels during the time interval Δt, enabling the cancer cells to overcome the defenses of the immune system. I will refer to these aspects of the immune system as the critical aspects of the immune system for that tumor in the individual. For example, these aspects could be the cytotoxicity of natural killer (NK) cells and/or the NK-cell numbers. If the critical aspects of the immune system had been boosted so that they did not fall below the critical levels, the uncontrolled multiplication of the cancer cells and the development of the malignant tumor may have been prevented.

The same concept may be applicable for treating cancer also. If the critical aspects of the immune system for all the tumors in a cancer patient are boosted so that they are raised and maintained above the critical levels, the uncontrolled multiplication of the cancer cells may cease and the immune system may be able to eliminate the cancer cells or keep them under control.

Interventions to boost the immune system

A large variety of interventions are known to boost the immune system(Doss 2019), e.g., exercise(Fairey et al. 2005), flu vaccination(Levin 2012), cholera vaccination(Majumder 2015), fruit-vegetable diet(Gibson et al. 2012), reducing red meat in diet(Cao et al. 2018), aspirin(Plescia et al. 1975), statins(Gruenbacher et al. 2010), smoking cessation(Mili et al. 1991), rhythmic breathing(Kochupillai et al. 2005), Vitamin D supplementation(Aranow 2011), hyperthermia(Farjadian et al. 2013), and living at a high elevation(Mishra et al. 2010). In the cited studies, different interventions have been observed to enhance different aspects of the immune system, and some aspects of the immune system were not enhanced by some of the interventions. For example, as reported in a compilation of the effects of exercise on the aging immune system(Simpson et al. 2012), whereas some of the studies showed enhancement of NK-cell cytotoxicity, T-cell proliferation, IFN-γ, CD4+ T-cell counts, or CD8+ T-cell counts following the interventions, other studies did not show increase in these aspects. Another example is that the interventions of rhythmic breathing(Kochupillai, Kumar et al. 2005) and living at a high elevation(Mishra and Ganju 2010) increased the NK-cell numbers but exercise in breast cancer survivors(Fairey, Courneya et al. 2005) and radon spa therapy(Ruhle et al. 2017) did not. In addition to such reported variability in the average responses to the different immune boosting interventions, the nature of the immune system response in any particular individual may also depend on the individual's gender, age, the intensity and frequency of the interventions, genetic factors, etc.

The need for multiple interventions

We do not know what the critical aspects of the immune system are for any particular malignant tumor that may develop or has developed in an individual and which interventions would boost the critical aspects in that individual. Therefore, in order to increase the likelihood that the critical aspects of the immune system are enhanced for all the developing and/or developed tumors in the individual, it may be advisable to use many different interventions that boost the immune system.

For some of the interventions, though the critical aspects are enhanced by the interventions, the magnitudes of the enhancements may not be sufficient to raise them above the critical levels. However, if several such interventions were utilized and their effects combined, the magnitudes of the enhancements could be sufficient to raise them above the critical levels resulting in a synergistic cancer preventive and/or therapeutic effect.

Since cancer is immunosuppressive(Whiteside 2006), for the individuals who have diagnosed or undiagnosed cancer, more immune system boosting interventions may be needed for overcoming the immune suppression and elevating the critical aspects of the immune system above the critical levels.

Due to these reasons, it may be advisable to utilize as many of the immune system boosting interventions as practicable.

Although many interventions are known to boost the immune system, not all the interventions would be applicable or acceptable to everyone, and so the list of interventions would need to be individualized based on individual circumstances and preferences. I am referring to this approach

as “Individualized Interventions to Improve the Immune Response”, or the I^4R approach(Doss 2019).

Effect of individual interventions on cancer

The effect of using multiple immune boosting interventions on cancer is not known but the effect of using some of the individual interventions has been reported. Many of the individual immune system boosting interventions have been observed to reduce the cancer incidence and mortality rates for the general population (Tables 1 and 2) and the mortality rates for cancer patients (Table 3).

Table 1: The effect of immune system boosting interventions on cancer incidence in the public.

Immune system boosting intervention	Details of the study and the cohorts compared	Relative risk for cancer incidence, with the 95% confidence intervals (CIs) shown in parentheses.
Physical activity(Orsini et al. 2008)	Men residing in 2 counties in central Sweden: Men who walked or bicycled for 60-90 minutes per day compared to those who hardly walked or bicycled	0.84 (0.72, 0.98)
Smoking cessation(Saito et al. 2017)	A pooled analysis of eight studies in Japan: Men who stopped smoking for 21+ years compared to those who continued to smoke	0.64 (0.57, 0.71)
Fruit-vegetable intake(Boffetta et al. 2010)	European cohort of men and women aged 25-70: Those consuming >647 gm of fruits and vegetables per day compared to those consuming <227 gm per day	0.89 (0.85, 0.93)
Statin use(Karp et al. 2008)	Patients post-acute myocardial Infarction: those taking high-dose statins compared to those taking no statins	0.75 (0.60, 0.95)
Aspirin use(Qiao et al. 2018)	A meta-analysis of 218 studies: those who used daily aspirin compared to those who did not	0.89 (0.87, 0.91)
Plasma Vitamin D level modification with sunlight, diet, supplements, etc.(Giovannucci et al. 2006)	Male health professionals: Those with higher projected Vitamin D levels compared to those with lower levels	0.83 (0.74, 0.92)

Table 2. The effect of immune system boosting interventions on cancer mortality in the public

Immune system boosting intervention	Details of the study and the cohorts compared	Relative risk for cancer mortality, with the 95% CIs shown in parentheses.
Exercise	Study of Korean men and women 20 year and older: those with the highest physical activity compared to those with the least physical activity(Jee et al. 2018)	0.73 (0.69, 0.78)
Statin use	Women aged 50–79 years: statin users compared to nonusers(Wang et al. 2016)	0.78 (0.71, 0.86)
Smoking cessation	26-year follow-up of U.S. veterans: former smokers compared to current smokers(McLaughlin et al. 1995)	0.62 (0.60, 0.64)
Influenza vaccination	Elderly population of a county in southern Taiwan: those vaccinated for influenza compared to those not vaccinated(Wang et al. 2007)	0.74 (0.64, 0.86)
Fruit-vegetable consumption	A meta-analysis of 95 studies: those who consumed 500 gm of fruits and vegetables per day compared to those consuming no fruits or vegetables(Aune et al. 2017)	0.87 (0.84, 0.90)
Vitamin D supplementation	Meta-analyses of 5 randomized controlled trials of vitamin D supplementation: those having vitamin D supplementation compared to those having placebo(Keum et al. 2019)	0.87 (0.79, 0.96)
Reduction of consumption of unprocessed red meat	Meta-analysis of 7 studies: reduction of 3 servings of unprocessed red meat per week(Han et al. 2019)	0.92 (0.89, 0.94)

Table 3. The effect of immune system boosting interventions on mortality in cancer patients.

Immune system boosting intervention	Details of the study and the cohorts compared	Relative risk for mortality, with the 95% CIs shown in parentheses.
Physical activity	Men diagnosed with any cancer: those with the highest level of physical activity compared to those with the lowest level(Lee et al. 2014)	0·52 (0·42, 0·65)
Cholera vaccination	Prostate cancer patients: patients vaccinated for cholera compared to those not vaccinated(Ji et al. 2018)	0·53 (0·41, 0·69)
Hyperthermia	Patients with loco-regionally advanced cervical cancer: those having hyperthermia	0·60 (0·38, 0·95)

	plus radiation therapy compared to those having radiation therapy alone(Franckena et al. 2008)	
Fruits-vegetables in diet	Colorectal cancer patients: patients having the highest uptake of fruits-vegetables compared to those having the lowest uptake(Guinter et al. 2018)	0·62 (0·47, 0·83)
Statin use	A meta-analysis of 55 studies of cancer patients: statin users compared to non-users(Mei et al. 2017)	0·70 (0·66, 0·74)
Daily aspirin	Colorectal cancer patients: patients having daily aspirin compared to patients having placebo(Elwood et al. 2016)	0·81 (0·73, 0·89)
Smoking cessation	Patients diagnosed with cancer: patients who quit smoking compared to those who continued to smoke(Warren et al. 2013)	0·85 (0·75, 0·96)

Effect of multiple immune boosting interventions

If multiple interventions are utilized, considering the results from the use of the individual interventions noted in Tables 1-3, much greater reduction of the cancer incidence and mortality rates in the general public and the mortality rates in the cancer patients may be achievable. For example, if all the interventions listed in Table 1 (or 2) are applicable for some individuals in the general population and they agree to utilize the interventions, assuming that the effects of the different interventions are not correlated, the relative risk for cancer incidence (or mortality) from utilizing all the listed interventions in the respective Tables would be the product of the individual relative risks, and would be 0.27 (95% CI: 0.18, 0.35) for cancer incidence and 0.18 (95% CI: 0.14, 0.22) for cancer mortality. Similarly, if all the interventions listed in Table 3 are applicable for some cancer patients and they agree to utilize them, assuming that the observed reductions in the mortality rates following the different interventions are uncorrelated and would be applicable for different types of cancers, the relative risk of mortality for the cancer patients from the utilization of the listed interventions would be the product of the individual relative risks, and is calculated to be 0.049 (95% CI: 0.016, 0.082).

Though these are rough estimates due to the simplifying assumptions made in deriving them, the large projected reductions in the adverse impact of cancer - the 73% reduction in the cancer incidence and the 82% reduction in the cancer mortality for the general public and the 95% reduction in the mortality rate of the cancer patients - with the use of the multiple interventions is indicative of the tremendous power of this approach. Many more interventions are known to boost the immune system(Doss 2019) and these interventions may also have cancer preventive and/or therapeutic effects which may reduce the above calculated relative risks even further.

One of the limitations of this approach is that if certain cancer cells are able to evade the immune system and multiply uncontrollably in spite of the enhanced immune system, the consequent tumors would not be treated effectively by the I^4R approach.

Since cancer suppresses the immune system, we can expect that the immune boosting interventions with the I^4R approach would be more effective in treating early-stage cancers than late-stage cancers. However, there are indeed examples of metastatic tumors being eliminated by individual immune system boosting interventions. In Coley's report on the treatment of patients with inoperable sarcomas using mixed bacteria vaccine, over 2/3 of the patients were free from the disease in the follow-up for period, which ranged from 6 to 16 years(Coley 1910). The improved survival of cancer patients following the individual immune boosting interventions (Table 3) indicates that the interventions reduced or eliminated metastatic disease, since reduction of metastases is needed for improving cancer patient survival. These examples indicate that late-stage cancers may also be amenable to effective treatment with the immune system boosting interventions under the I^4R approach. It is likely that more immune system boosting interventions would be needed for the effective treatment of metastatic cancers as compared to the interventions needed for the effective treatment of early-stage cancers. Clinical trials are needed to determine for which cancer types and stages the I^4R approach is effective and results in better outcomes than the traditional treatments.

Advantages of the I^4R approach

The I^4R approach for cancer treatment has many major advantages for the cancer patients and their families in comparison to the traditional cancer treatments. One major advantage of the approach is that there would be few adverse side effects from the immune system boosting interventions. Another major advantage is that most of the interventions are not very expensive and so the financial toxicities currently experienced by the cancer patients and their families would be reduced. A third advantage is that many of the interventions would improve other aspects of the patients' health, in addition to reducing the cancer burden of the patients. For example, exercise would improve cardiovascular health in addition to boosting the immune system and having a cancer therapeutic effect. A fourth advantage is that the treatments would have a cancer preventive effect in contrast to the carcinogenic effect of some of the traditional treatments. In view of the advantages, clinical trials of the I^4R approach should be conducted promptly so that if the approach is found to be valid, it can be adopted for the benefit of the patients. For any types and stages of cancers for which the I^4R approach is found to be ineffective, the traditional treatments would need to be utilized.

Discussion

My hypothesis is that clinical cancer develops when some aspects of the immune system fall below certain critical levels. Since small decreases in the aspects of the immune system, which may be too small to measure reliably due to the errors in the measurements, may be sufficient to lower them below the critical levels during a period of time leading to the uncontrolled multiplication of cancer cells and the development of a tumor, and also since we do not know which aspects of the immune system are the critical aspects for a particular tumor, it would not be feasible to test the hypothesis by confirming the occurrence of a tumor following the decline of some aspects of the immune system below the critical levels. Even though the hypothesis cannot be tested directly, it has led to an approach for preventing and treating cancer using multiple immune system boosting interventions. Success in preventing and treating cancer with multiple immune system boosting interventions under the I^4R approach would validate the proposed hypothesis that clinical cancer develops when critical aspects of the immune system fall below certain critical levels.

Implications for public health

Cancer continues to adversely affect millions worldwide every year due to the ineffectiveness of the traditional treatments for many patients and the adverse side effects for the increasing number of cancer survivors. If the results from the clinical trials justify it, the widespread adoption of the I^4R approach may allow us to realize the goal of reducing the death and suffering from cancer in the world.

Conflict of interest statement

I declare that I have no conflicts of interest.

Disclaimer

The views expressed by the author in this article are his personal views and do not necessarily represent those of his employer.

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