 doi:10.20944/preprints201912.0269.v1

Type of publication:
Hypothesis

Title:
Cancer Prevention and Treatment with Immune System Boosting Interventions

Author:
Mohan Doss, Diagnostic Imaging, Fox Chase Cancer Center, Philadelphia, PA, USA

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, more 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.

Keywords:
Cancer, Cancer prevention, Cancer therapy, Immune boosting interventions

Corresponding Author:
Mohan Doss, Diagnostic Imaging, Fox Chase Cancer Center, 333 Cottman Avenue, Philadelphia, PA, 19111, USA. Email: mohan.doss@fccc.edu Phone: +1 215 214-1707

 doi:10.20944/preprints201912.0269.v1

Hypothesis

Cancer Prevention and Treatment with Immune System Boosting Interventions

Background

The war on cancer has been fought during the past several decades primarily based on the somatic mutation model of cancer[1]. Even though many advances have taken place in the cancer field[2], there are indications that we are far from winning the war on cancer[3]. Age-adjusted cancer mortality rate continue to be high[4] and cancer has become the leading cause of death in high income countries, overtaking heart disease[5]. The cancer drugs that have been approved for use in the recent years are very expensive but have led to a median gain of only 2.1 months in the overall survival of cancer patients[6]. The adverse side effects of the cancer treatments are affecting the quality of life[7] of the increasing number of cancer survivors[8]. Cancer patients and their families also face substantial financial toxicities due to the high costs of the treatments[9]. Though there has been a small and steady reduction of the cancer mortality rate in the USA since the early 1990s[4], much of the decrease may be attributed to the reduction in smoking that began in the 1960s[10], 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, an approach based on the immune suppression model of cancer[11] is discussed.

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[12] and young organ-transplant recipients[13]. 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[14], which almost everyone has[15]. 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. This concept for the development of cancer has been called the immune suppression model of cancer[11]. In a prospective study of adults aged 40 and over[16], 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[17].

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[18-20], 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.

 doi:10.20944/preprints201912.0269.v1

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. These aspects of the immune system may be labelled 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[17], e.g., exercise[21], influenza vaccination[22], cholera vaccination[23], exposure to low-level radiation[24], radon spa therapy[25], fruit-vegetable diet[26], reducing red meat in diet[27], aspirin[28], statins[29], smoking cessation[30], rhythmic breathing[31], Vitamin D supplementation[32], hyperthermia[33], and living at a high elevation[34]. 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[35], 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[31] and living at a high elevation[34] increased the NK-cell numbers but exercise in breast cancer survivors[21] and radon spa therapy[25] 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.

Even when the critical aspects are enhanced by some of 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.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 December 2019 doi:10.20944/preprints201912.0269.v1

Since cancer is immunosuppressive[36], 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. This approach is known as "Individualized Interventions to Improve the Immune Response", or the I[4]R approach[17].

Effect of individual interventions on cancer

The effect of using multiple immune system 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, respectively) 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[37]	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[38]	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[39]	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[40]	Patients post-acute myocardial	0.75 (0.60, 0.95)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 December 2019 doi:10.20944/preprints201912.0269.v1

	infarction: those taking high-dose statins compared to those taking no statins.	
Aspirin use[41]	A meta-analysis of 218 studies: those who used daily aspirin compared to those who did not.	0.89 (0.87, 0.91)
Exposure to low-level radiation[42]	Apartment residents in Taiwan: those who were exposed to low-level radiation due to radioactively contaminated steel used in the building compared to an equivalent Taiwanese population group.	0.84 (0.74, 0.95)
Elevation of plasma Vitamin D level with sunlight, diet, supplements, etc.	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[43]	Study of Korean men and women 20 year and older: those with the highest physical activity compared to those with the least physical activity.	0.73 (0.69, 0.78)
Statin use[44]	Women aged 50–79 years: statin users compared to nonusers.	0.78 (0.71, 0.86)
Smoking cessation[45]	26-year follow-up of U.S. veterans: former smokers compared to current smokers.	0.62 (0.60, 0.64)
Influenza vaccination[46]	Elderly population of a county in southern Taiwan: those vaccinated for influenza compared to those not vaccinated.	0.74 (0.64, 0.86)
Exposure to low-level ionizing radiation[47]	Nuclear shipyard workers: those who were exposed to low-level ionizing radiation compared to workers who were not exposed to the radiation.	0.85 (0.79, 0.91)
Fruit-vegetable consumption[48]	A meta-analysis of 95 studies: those who consumed 500 gm of fruits and	0.87 (0.84, 0.90)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 December 2019 doi:10.20944/preprints201912.0269.v1

	vegetables per day compared to those consuming no fruits or vegetables.	
Vitamin D supplementation[49]	Meta-analyses of 5 randomized controlled trials of vitamin D supplementation: those having vitamin D supplementation compared to those having placebo.	0.87 (0.79, 0.96)
Reduction of consumption of unprocessed red meat[50]	Meta-analysis of 7 studies: reduction of 3 servings of unprocessed red meat per week.	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[51]	Men diagnosed with any cancer: those with the highest level of physical activity compared to those with the lowest level.	0·52 (0·42, 0·65)
Cholera vaccination[52]	Prostate cancer patients: patients vaccinated for cholera compared to those not vaccinated.	0·53 (0·41, 0·69)
Hyperthermia[53]	Patients with loco-regionally advanced cervical cancer: those having hyperthermia plus radiation therapy compared to those having radiation therapy alone.	0·60 (0·38, 0·95)
Fruits-vegetables in diet[54]	Colorectal cancer patients: patients having the highest uptake of fruits-vegetables compared to those having the lowest uptake.	0·62 (0·47, 0·83)
Statin use[55]	A meta-analysis of 55 studies of cancer patients: statin users compared to nonusers.	0·70 (0·66, 0·74)
Daily aspirin[56]	Colorectal cancer patients: patients having daily aspirin compared to patients having placebo.	0·81 (0·73, 0·89)
Smoking cessation[57]	Patients diagnosed with cancer: patients who quit smoking compared to those who continued to smoke.	0·85 (0·75, 0·96)
Repeated exposures to low-level ionizing radiation[58]	Patients with non-Hodgkin's lymphoma: those treated with repeated exposures to low-level ionizing radiation over five weeks compared to patients treated with chemotherapy[58], with correction for generating the comparison to untreated cancer patients, using a nominal relative risk for mortality of 0·76 following chemotherapy[59].	0·43 (0·15, 0·70)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 20 December 2019 doi:10.20944/preprints201912.0269.v1

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, 0.36) for cancer incidence and 0.15 (95% CI: 0.12, 0.19) 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 0·021 (95% CI: 0·0015, 0·041).

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 85% reduction in the cancer mortality for the general public and the 98% 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[17] 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, it is likely that the immune system boosting interventions under the I^4R approach would be more effective in treating early-stage cancers than late-stage cancers. However, there are 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 period, which ranged from 6 to 16 years[60]. The improved survival of cancer patients following the individual immune system 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

 doi:10.20944/preprints201912.0269.v1

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. 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

The hypothesis proposed in this article 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.

References

1. Tomasetti, C., Li, L. & Vogelstein, B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* **355**, 1330-1334 (2017).
2. Heymach, J. *et al.* Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol* **36**, 1020-1044 (2018).
3. Leaf, C. *The Truth in Small Doses: Why We're Losing the War on Cancer-and How to Win It* (Simon and Schuster, New York, 2014).
4. Xu, J., Murphy, S. L., Kochanek, K. D., Bastian, B. & Arias, E. Deaths: Final Data for 2016. *Natl Vital Stat Rep* **67**, 1-76 (2018).
5. Dagenais, G. R. *et al.* Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* (2019).

6. Fojo, T., Mailankody, S. & Lo, A. Unintended consequences of expensive cancer therapeutics-the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg* **140**, 1225-1236 (2014).
7. Langbaum, T. & Smith, T. J. Time to Study Metastatic-Cancer Survivorship. *N Engl J Med* **380**, 1300-1302 (2019).
8. Bluethmann, S. M., Mariotto, A. B. & Rowland, J. H. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. *Cancer Epidemiol Biomarkers Prev* **25**, 1029-1036 (2016).
9. Gordon, L. G., Merollini, K. M. D., Lowe, A. & Chan, R. J. A Systematic Review of Financial Toxicity Among Cancer Survivors: We Can't Pay the Co-Pay. *The Patient - Patient-Centered Outcomes Research* **10**, 295-309 (2017).
10. Thun, M. J. & Jemal, A. How much of the decrease in cancer death rates in the United States is attributable to reductions in tobacco smoking? *Tob Control* **15**, 345-347 (2006).
11. Doss, M. Changing the Paradigm of Cancer Screening, Prevention, and Treatment. *Dose Response* **14**, 1559325816680539 (2016).
12. Biggar, R. J., Frisch, M. & Goedert, J. J. Risk of cancer in children with AIDS. AIDS-Cancer Match Registry Study Group. *JAMA* **284**, 205-209 (2000).
13. Acuna, S. A. *et al.* Cancer Mortality among recipients of solid-organ transplantation in Ontario, Canada. *JAMA Oncol* **2**, 463-469 (2016).
14. Koebel, C. M. *et al.* Adaptive immunity maintains occult cancer in an equilibrium state. *Nature* **450**, 903-907 (2007).
15. Greaves, M. Does everyone develop covert cancer? *Nat Rev Cancer* **14**, 209-210 (2014).
16. Imai, K., Matsuyama, S., Miyake, S., Suga, K. & Nakachi, K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet* **356**, 1795-1799 (2000).
17. Doss, M. *Your Custom Roadmap for Potentially Preventing and Curing Cancer* (Mohan Doss, Philadelphia, 2019).
18. Lewis, V. M., Twomey, J. J., Bealmear, P., Goldstein, G. & Good, R. A. Age, thymic involution, and circulating thymic hormone activity. *J Clin Endocrinol Metab* **47**, 145-150 (1978).
19. Hazeldine, J., Hampson, P. & Lord, J. M. Reduced release and binding of perforin at the immunological synapse underlies the age-related decline in natural killer cell cytotoxicity. *Aging Cell* **11**, 751-759 (2012).
20. Kubota, K. *et al.* [Changes in the blood cell counts with aging]. *Nihon Ronen Igakkai Zasshi* **28**, 509-514 (1991).
21. Fairey, A. S. *et al.* Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. *J Appl Physiol (1985)* **98**, 1534-1540 (2005).
22. Levin, M. J. Immune senescence and vaccines to prevent herpes zoster in older persons. *Curr Opin Immunol* **24**, 494-500 (2012).
23. Majumder, P. P. Genomics of immune response to typhoid and cholera vaccines. *Philos Trans R Soc Lond B Biol Sci* **370** (2015).
24. Yang, G. *et al.* Low-dose ionizing radiation induces direct activation of natural killer cells and provides a novel approach for adoptive cellular immunotherapy. *Cancer biotherapy & radiopharmaceuticals* **29**, 428-434 (2014).

25. Ruhle, P. F. *et al.* Modulation of the peripheral immune system after low-dose radon spa therapy: Detailed longitudinal immune monitoring of patients within the RAD-ON01 study. *Autoimmunity* **50**, 133-140 (2017).
26. Gibson, A. *et al.* Effect of fruit and vegetable consumption on immune function in older people: a randomized controlled trial. *Am J Clin Nutr* **96**, 1429-1436 (2012).
27. Cao, Y. *et al.* Meat intake and risk of diverticulitis among men. *Gut* **67**, 466-472 (2018).
28. Plescia, O. J., Smith, A. H. & Grinwich, K. Subversion of immune system by tumor cells and role of prostaglandins. *Proc Natl Acad Sci U S A* **72**, 1848-1851 (1975).
29. Gruenbacher, G. *et al.* IL-2 costimulation enables statin-mediated activation of human NK cells, preferentially through a mechanism involving CD56+ dendritic cells. *Cancer Res* **70**, 9611-9620 (2010).
30. Mili, F., Flanders, W. D., Boring, J. R., Annest, J. L. & Destefano, F. The associations of race, cigarette smoking, and smoking cessation to measures of the immune system in middle-aged men. *Clinical Immunology and Immunopathology* **59**, 187-200 (1991).
31. Kochupillai, V. *et al.* Effect of rhythmic breathing (Sudarshan Kriya and Pranayam) on immune functions and tobacco addiction. *Ann N Y Acad Sci* **1056**, 242-252 (2005).
32. Aranow, C. Vitamin D and the immune system. *J Investig Med* **59**, 881-886 (2011).
33. Farjadian, S., Norouzian, M., Younesi, V., Ebrahimpour, A. & Lotfi, R. Hyperthermia increases natural killer cell cytotoxicity against SW-872 liposarcoma cell line. *Iran J Immunol* **10**, 93-102 (2013).
34. Mishra, K. P. & Ganju, L. Influence of high altitude exposure on the immune system: a review. *Immunol Invest* **39**, 219-234 (2010).
35. Simpson, R. J. *et al.* Exercise and the aging immune system. *Ageing Res Rev* **11**, 404-420 (2012).
36. Whiteside, T. L. Immune suppression in cancer: effects on immune cells, mechanisms and future therapeutic intervention. *Semin Cancer Biol* **16**, 3-15 (2006).
37. Orsini, N., Mantzoros, C. S. & Wolk, A. Association of physical activity with cancer incidence, mortality, and survival: a population-based study of men. *Br J Cancer* **98**, 1864-1869 (2008).
38. Saito, E. *et al.* Smoking cessation and subsequent risk of cancer: A pooled analysis of eight population-based cohort studies in Japan. *Cancer Epidemiol* **51**, 98-108 (2017).
39. Boffetta, P. *et al.* Fruit and Vegetable Intake and Overall Cancer Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *JNCI: Journal of the National Cancer Institute* **102**, 529-537 (2010).
40. Karp, I., Behlouli, H., Lelorier, J. & Pilote, L. Statins and cancer risk. *Am J Med* **121**, 302-309 (2008).
41. Qiao, Y. *et al.* Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. *BMC Cancer* **18**, 288 (2018).
42. Doss, M. Comment on '30 years follow-up and increased risks of breast cancer and leukaemia after long-term low-dose-rate radiation exposure'. *Br J Cancer* **118**, e9 (2018).
43. Jee, Y., Kim, Y., Jee, S. H. & Ryu, M. Exercise and cancer mortality in Korean men and women: a prospective cohort study. *BMC Public Health* **18**, 761 (2018).
44. Wang, A. *et al.* Statin use and all-cancer survival: prospective results from the Women's Health Initiative. *British Journal of Cancer* **115**, 129-135 (2016).

45. McLaughlin, J. K., Hrubsec, Z., Blot, W. J. & Fraumeni Jr., J. F. Smoking and cancer mortality among U.S. veterans: A 26-year follow-up. *International Journal of Cancer* **60**, 190-193 (1995).
46. Wang, C. S., Wang, S. T., Lai, C. T., Lin, L. J. & Chou, P. Impact of influenza vaccination on major cause-specific mortality. *Vaccine* **25**, 1196-1203 (2007).
47. Sponsler, R. & Cameron, J. R. Nuclear shipyard worker study (1980-1988): a large cohort exposed to low-dose-rate gamma radiation. *Int J Low Radiat* **1**, 463-478 (2005).
48. Aune, D. *et al.* Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int J Epidemiol* **46**, 1029-1056 (2017).
49. Keum, N., Lee, D. H., Greenwood, D. C., Manson, J. E. & Giovannucci, E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Ann Oncol* **30**, 733-743 (2019).
50. Han, M. A. *et al.* Reduction of Red and Processed Meat Intake and Cancer Mortality and Incidence: A Systematic Review and Meta-analysis of Cohort Studies. *Annals of Internal Medicine* **171**, 711-720 (2019).
51. Lee, I. M., Wolin, K. Y., Freeman, S. E., Sattlemair, J. & Sesso, H. D. Physical activity and survival after cancer diagnosis in men. *J Phys Act Health* **11**, 85-90 (2014).
52. Ji, J., Sundquist, J. & Sundquist, K. Association between post-diagnostic use of cholera vaccine and risk of death in prostate cancer patients. *Nat Commun* **9**, 2367-2367 (2018).
53. Franckena, M. *et al.* Long-term improvement in treatment outcome after radiotherapy and hyperthermia in locoregionally advanced cervix cancer: an update of the Dutch Deep Hyperthermia Trial. *Int J Radiat Oncol Biol Phys* **70**, 1176-1182 (2008).
54. Guinter, M. A., McCullough, M. L., Gapstur, S. M. & Campbell, P. T. Associations of Pre- and Postdiagnosis Diet Quality With Risk of Mortality Among Men and Women With Colorectal Cancer. *J Clin Oncol*, JCO1800714 (2018).
55. Mei, Z. *et al.* Effects of statins on cancer mortality and progression: A systematic review and meta-analysis of 95 cohorts including 1,111,407 individuals. *Int J Cancer* **140**, 1068-1081 (2017).
56. Elwood, P. C. *et al.* Aspirin in the Treatment of Cancer: Reductions in Metastatic Spread and in Mortality: A Systematic Review and Meta-Analyses of Published Studies. *PLoS One* **11**, e0152402 (2016).
57. Warren, G. W., Kasza, K. A., Reid, M. E., Cummings, K. M. & Marshall, J. R. Smoking at diagnosis and survival in cancer patients. *Int J Cancer* **132**, 401-410 (2013).
58. Pollycove, M. Radiobiological Basis of Low-Dose Irradiation in Prevention and Therapy of Cancer. *Dose-Response* **5**, 26-38 (2007).
59. Huchcroft, S. A. & Snodgrass, T. Cancer patients who refuse treatment. *Cancer Causes Control* **4**, 179-185 (1993).
60. Coley, W. B. The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus). *Proc R Soc Med* **3**, 1-48 (1910).

Acknowledgments:
This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA006927.

Competing interests:
Financial competing interests: None.
Non-financial competing interests: I am the President of the I4R Foundation, a nonprofit organization whose mission is to promote education and research on the I^4R approach that is discussed in the manuscript.

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

Author contributions:
M.D. conceived of the work, studied the literature, analyzed the information, and wrote the manuscript.

Correspondence:
Correspondence should be addressed to M.D. (mohan.doss@fccc.edu)