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# Expanding the role of 'cancer prevention' in clinical trials design and analysis

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"...active participation by preventionists and clinical trialists in the design and analysis of cutting edge clinical trials will result in the identification of more effective strategies to improve outcomes for cancer patients across disease sites."

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## The problem at hand

Survival for cancer patients has improved through the identification of potentially effective biologic targets and development of new clinical therapies directed at these targets. Significant advances over the past decades have resulted in improved survival for virtually all cancer disease sites resulting in an estimated 13 million cancer survivors in the USA [1]. However, the advances of ever increasingly complex cancer care may suffer from a 10,000 foot view: the perceived importance of expensive therapeutics may overshadow a clinically meaningful variable common to large groups of cancer patients while the absolute benefit of a clinically meaningful variable associated with many cancer patients may substantially overshadow the benefit of an expensive therapy.

Obviously, cancer prevention is the most effective cancer treatment. Hundreds of studies have associated cancer risk with tobacco use, obesity, physical activity, and alcohol [2–4]. Perhaps the most well-studied cancer prevention activity is the avoidance or cessation of tobacco use [5]. Recent reports demonstrate that smoking increases the risk of developing cancer as well as several other diseases leading to significant reductions in life expectancy [5]. Smoking cessation reverses many of the cancer risks associated with tobacco use [6]. The cost–effectiveness of preventing smoking and increasing smoking cessation activities is far better than the cost–effectiveness of cancer treatment. Moreover, tobacco use decreases the effectiveness of cancer treatment and increases the risk of developing a second cancer [7–12], a fact that has not yet been incorporated into the cost–effectiveness of cancer treatment. Unfortunately, tobacco assessment and cessation are not included in the design or analysis of most clinical trials [13]. As this case-in-point demonstrates, perhaps the most well-studied and effective cancer prevention activity (tobacco use) is not being assessed or addressed as a standard part of clinical cancer research. The question arises if other common prevention variables may continue to have an effect in cancer patients.

## Confounding & effect modification

Confounding is an inaccuracy in the estimation of an association between a cause and outcome due to the presence of additional variables that may also be associated with an outcome. For confounding to exist, it cannot be in the stepwise causation pathway between the exposure of interest and outcome. For example, smoking is a well-known risk factor for the development of lung cancer [5]. One might assume that simply accounting for smoking alone will result in a complete picture of lung cancer risk. However, radon is also a risk factor for the development of lung

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cancer [14]. Both individually increase the risk of developing lung cancer and an individual does not require exposure to both in order to develop lung cancer.

Risk factors may interact, so that their associations with risk may depend on the presence or absence of other risk factors or exposures. Effect modification is a phenomenon whereby an exposure can alter the biologic effect of a risk factor thereby altering the risk of a specific outcome. If we again use the example of smoking and radon, whilst they both individually increase the risk of developing lung cancer, the risk is substantially higher (~25-times higher) in people who are exposed to radon and smoke [14]. As a result, smoking and radon exposure work together as effect modifiers for the development of lung cancer.

Several other studies demonstrate that obesity, activity, nutrition and alcohol may be associated with changes in outcomes for cancer patients [15–18]. In combination, many of these variables (tobacco included) may work in a synergistic or antagonistic fashion to increase the risk of developing a second cancer or alter the effectiveness of cancer treatment. For example, some data suggest that smoking may have a greater effect on mortality in obese cancer patients [19]. The risk of second cancer may be greater when tobacco is combined with alcohol use [20]. Considering additional complexities based upon gender, the adverse effect of tobacco on mortality in cancer patients may be more substantial in men than in women [8]. Notably, whereas cytotoxic cancer therapies may increase the risk of developing a second primary cancer, the combination of chemotherapy or radiotherapy with smoking dramatically increases the risk of developing a second primary cancer [10–12]. These are simply examples of how one or more variables may combine as potential effect modifiers for outcome in cancer patients.

## Considering the role of 'cancer prevention' in clinical trial design

Experts in cancer prevention are trained in the design and analysis of large trials to associate the risk of an exposure with outcome. As a term, 'cancer prevention' is traditionally associated with assessing the risk of developing cancer. However, with the growing population of cancer survivors, the utility of cancer prevention may extend to considering potential confounding or effect-modifying risks in cancer survivors associated with the risk of developing second cancers as well as risks associated with treatment related toxicity, cancer recurrence, and non-cancer specific morbidity (such as heart disease). Expanding consideration to these other important clinical variables can make preventionists extremely valuable for clinical trial design and analysis.

In the design of clinical trials, several variables may be excluded from analysis or consideration through randomization and comparing representative equivalence between randomization arms. This approach generally assumes equal distribution of confounding variables and is a commonly accepted method to reduce the effect of confounding. However, it does not account for potential effect modification. In addition, standard clinical trial design generally does not account for dynamic effect modifiers that may change during or following a cancer diagnosis. Importantly, exposure and changes in exposure to potential effect modifiers may not have the same effect. Whereas obesity prior to diagnosis correlates with poor outcome in cancer patients, BMI after diagnosis may not have an association with outcome [15]. In contrast, tobacco cessation reduces the risk of developing cancer in a time- and dose-dependent manner [6] and tobacco cessation can also reduce the associations between smoking and poor outcome in cancer patients [21,22]. Consequently, tracking potential effect modifiers may result in the identification of clinically important associations that may be very useful to increase the efficacy of cancer treatments.

There are several fundamental issues to consider in the implementation of a standardized approach toward assessing effect modification in clinical trials design:

- Assessments should be standardized for a specific effect modifier. Standardization should take into account the ability to accurately identify an effect modifier across disease sites and across cancer treatments. Efforts made to assess common outcomes (such as cardiac toxicity) in a standardized manner are needed;

- Exposures and prevention-related activities should be collected at diagnosis, during treatment and during follow up. However, data collection cannot be onerous. Practically speaking, standardized assessments should be tailored to cover as large a population of cancer patients as possible and collected on a reasonable follow-up schedule. For instance, whereas collection in an intensive chemotherapy trial for lung cancer may be reasonable on a biweekly or monthly basis, it would be difficult to justify data collection in a trial for low-to-moderate-risk prostate cancer patients more frequently than every 3–6 months. Collection of standardized information according to the temporal requirements of a specific trial is likely far more useful (and less burdensome) than attempting to change trial design to fit a specific temporal pattern;

- Data should be collected in an efficient manner. Again, for practical reasons, large complex assessments

will present a significant burden for clinical trialists and patients enrolled on clinical trials. Standardized assessments should be minimized to promote accurate data collection for the majority of cancer patients. Additional variables that are restricted to small subsets of cancer patients are likely not to be useful variables. The authors suggest consideration of tobacco use, alcohol, obesity, nutrition, and physical activity as potential effect modifiers that could be standardized across disease sites and cancer treatments. However, cooperative groups could convene panels to consider pertinent variables;

- Whenever possible, data should be centralized and combined for pooled analyses across disease sites for common outcomes. Clinical trialists should have access to trained personnel who can effectively analyze collected data (such as heart disease and risk of developing a second cancer). At the same time, experts in specific disease sites and cancer-related outcomes must be available to participate in these analyses. Disease-specific oncologists need to collaborate with prevention researchers with expertise in tobacco, alcohol, obesity, physical activity and diet to best evaluate the impact of these factors on treatment outcome;

- Consideration should be given to analyses performed in a timely manner. Pooled analyses from several trials may demonstrate a clinically meaningful health risk (or benefit) long before the final closure of a clinical trial. As a result, patients enrolled on clinical trials, as well as patients currently receiving standard cancer treatment, may benefit from an intervention months or years prior to completion of a trial. However, this last consideration may run counter to the principles of blinding in clinical trials and would almost certainly raise concerns by clinical trialists. At the same time, interim efficacy analyses are common to clinical trials, and data stored in a centralized manner may permit timely analyses without prematurely revealing randomization to investigators participating in blinded trials.

Cancer care is in a continuous state of transition. Embarking on a standardized method to assess potential effect modifiers for cancer treatment will represent a significant advance in our approach to cutting edge research. Undoubtedly, there will be several obstacles to the implementation of this approach. Data sharing and the pooling of data from multiple studies may simultaneously identify exposures that modify the impact of therapy; however, data sharing may be challenging if it runs counter to proprietary interests. At the same time, this approach will further clarify the effectiveness of cancer therapeutics and simultaneously identify patient cohorts that can serve as a rich resource to develop future targeted therapeutics. The collection of additional data will also require additional costs; however, prospective standardization of data collection in combination with no alterations in the temporal aspects of a clinical trial should minimize any additional costs.

Incorporating active participation of preventionists into clinical trials design and analysis will undoubtedly require 'give and take' from both prevention and therapeutic researchers. However, active participation by preventionists and clinical trialists in the design and analysis of cutting edge clinical trials will result in the identification of more effective strategies to improve outcomes for cancer patients across disease sites.

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