Published in final edited form as:

JAMA. 2009 November 18; 302(19): 2152–2153. doi:10.1001/jama.2009.1691.

Assessing cancer prevention studies - a matter of time

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To reduce the incidence of neural tube defects, the US Food and Drug Administration (FDA) mandated folic acid fortification of flour and other grains beginning in 1998.¹ Subsequent studies showed an overall increase in mean folic acid levels among US residents.^{2, 3} Within a few years of this mandate, a decrease in the incidence of neural tube defects was noted in newborn infants.⁴ However, longer-term benefits of FA fortification for disease prevention⁵ including multiple cancers^{6–8} remain to be documented. Animal studies suggest that modest supplementation can reduce carcinogenesis. On the other hand, high doses of FA may speed cell division and increase tumor progression in preneoplastic lesions.^{9, 10} Better understanding of time frame and dosage is key to balancing risk and benefits.

In this issue of JAMA, Ebbing et al¹¹ present evidence of the association between FA treatment and cancer incidence and mortality, and all-cause mortality among persons in Norway, a country without FA food fortification. The study, a combined analysis of two randomized controlled trials (RCTs), evaluates an intervention with folic acid and B vitamins in high-risk cardiovascular disease patients as an adjunct to treatment to prevent recurrent cardiovascular disease or death after acute MI. The analysis addresses whether folic acid treatment in this group of patients is associated with a change in cancer incidence or mortality risk. Participants were randomized to one of four treatment groups containing a combination of FA 0.8mg, B₁₂ 0.4mg and vitamin B₆ 40mg. After a median of 39 months on trial and a further 38 months of voluntary follow-up, those receiving FA and B₁₂ were at increased risk of cancer diagnosis, cancer mortality, and all-cause mortality.

Understanding of time frame and dosage of FA administration will help to put these findings in context. There are three ways to address time frame: in the disease process, in exposure, and in study design.

As for the disease process, most cancers can be prevented with changes in lifestyle. How long it takes to achieve benefit from a change in lifestyle is not well understood. Folic acid fortification and neural tube defects are one clear example of the disease process. Results are relatively immediate because pre-conception and in utero exposures to folic acid lead to

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The authors declare they have no conflicts of interest

reduced birth defects in a 9-month window.¹² For cancer, on the other hand, a longer etiologic process means that causal and preventive exposures have a cumulative lifetime effect as cells progress from normal through accumulation of multiple genetic changes to final malignancy.

Evidence for cancer shows that average folic acid intake of US adults is inversely related to incidence.⁶ In a prospective analysis in which prediagnostic levels of plasma folic acid were measured, there were significant inverse associations with colorectal cancer-specific and overall mortality before and after US food fortification,⁸ with 50% reductions in mortality risk. The preventive benefits of folic acid on tumor initiation will decrease cancer initiation rates in a population that would have otherwise been susceptible without FA.¹³ Mortality rates will be lower decades later.

The current scientific evidence offers limited data on folic acid interacting with already present lesions in the short term. Plasma levels measured 2 or more years before diagnosis suggest no adverse effect on survival.⁶ Nor has the time frame been defined for inhibiting the development of new precursor lesions in the longer term. How such effects balance out at the population level will likely vary over time. To estimate these trade-offs at the population level requires knowledge of the proportion at each stage of progression from normal tissue to premalignant lesions to malignancy, which is currently unknowable.

Duration of exposure is most precisely measured for tobacco use, drugs and vitamins. For example, data from 2 RCTs of aspirin and incident colorectal cancer show no significant benefit after 10 years. However, after a median of 23 years of follow-up a significant reduction in colorectal cancer was observed.¹⁴

Duration of prevention studies is quite variable, but RCTs most often are short-term due to the demands on participants to comply with an intervention. Observational studies on the other hand can accumulate exposure over the life course. The randomized trial design may be most helpful to evaluate specific prevention research questions when the benefit will be observed shortly after the implementation of an intervention. These interventions may be able to be more tightly controlled in a short term study, and often lead to looking for effects that fit the time frame. By analogy, when keys are missing, it is common to look for them under the lamppost where there is light rather than in the murky location where the keys were more likely dropped. Lack of adherence over time further hinders this design for long-term prevention studies.

Long-term follow-up will often inform issues of duration of an intervention necessary to achieve a preventive benefit. For example, with the use of repeated measures, the duration and timing of exposure in the disease process can be measured more precisely. Clarifying the question being asked by different studies is essential for using the data to inform practice.

In addition, the intervention dosage and mean plasma folic acid levels in the US population as a whole^{2, 3, 8} are lower than the levels in the treatment group of the study by Ebbing et al¹¹ and other studies.¹⁵ Food fortification has led to an increased folic acid intake by an average of 100 µg/day and the proportion of adults reaching 400 µg/day is still below FDA

targets.³ According to data from NHANES, less than 4% of the population age 65 and older consume 1 mg/day or more of folic acid with the largest percentage of the population consuming between 0.3 and 0.4 mg/day.³ The intervention in the current trial (800 µg/day) among patients after myocardial infarction occurred in a folic acid-poor Norwegian population. Extrapolating from this high dosage to the US population is complex. However, US fortification appears to have left the population well within safe limits.

What do the results of the study by Ebbing et al.¹¹ mean for population health and for clinicians? The results indicate an excess of approximately 3.5 new cases of cancer per 1000 per year and 1 excess case of lung cancer per 1000 per year. The excess deaths correspond to 1.7 cancer deaths per 1000 per year. These numbers, if generalizable to the US, would be substantial at the overall level of total cancer incidence and mortality. Moreover, given the changes in blood levels of folic acid in the US, an increase in lung cancer incidence would be expected. However, rates for total cancer incidence decreased significantly from 2001 to 2005,¹⁶ and lung cancer incidence has also declined significantly in men over almost two decades and among women from the late 1990s.¹⁶ These national incidence rates do not support a substantial, population-wide adverse effect of the magnitude suggested in the study by Ebbing et al.

Preventive interventions require long-term evaluation. While the report by Ebbing et al. provides important short term data, the findings do not nullify the potential long-term benefits that folic acid fortification may have on population health. The time frame for benefit for some preventive interventions may span decades¹⁷, although smoking cessation may be unique among lifestyle changes that produce a rapid reduction in cancer risk.¹⁸

Cancer prevention efforts do not start or end with folic acid. Cessation of cigarette smoking for all who currently smoke and prevention of smoking in youth and adolescents remains the highest priority for cancer prevention. For those who do not smoke, eating a healthy diet and exercising to avoid weight gain or maintain weight loss will translate to lower risk of cancer, diabetes, and other chronic conditions. These are population-wide changes that take time, and the benefits of such lifestyle changes can take years, even decades to realize.

Acknowledgment

GAC is supported by an American Cancer Society Clinical Research Professorship and BFD is supported by PC081669 from the Department of Defense.

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