A conversation with Dr. Joshua Miller on January 8, 2016

Participants

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- Andrew Martin – Research Analyst, GiveWell
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Note: These notes were compiled by GiveWell and give an overview of the points made by Dr. Joshua Miller.

Summary

GiveWell spoke with Dr. Joshua Miller about folic acid and cancer risk. Conversation topics included the hypothesized dual relationship between folic acid (particularly excess intake of folic acid) and cancer risk, interpreting the results of a meta-analysis of randomized controlled trials (RCTs) of folic acid supplementation, and folic acid food fortification programs.

The dual relationship between folic acid and cancer risk

Folate (or its synthetic form, folic acid) is necessary for the growth and division of all cells, including cancer cells. Since antifolate drugs, which block folate metabolism, have successfully been used as chemotherapy treatments to suppress cancer growth, some researchers have hypothesized that folic acid intake (especially excess folic acid intake) could have the opposite effect, causing some types of existing cancer cells to proliferate more rapidly. However, there are also biological reasons to believe that folic acid can be protective against cancer initiation. The hypothesized dual relationship between folic acid and cancer risk is that it may accelerate the proliferation of existing cancer cells in some individuals, while protecting against cancer initiation in others.

Interpreting the results of a meta-analysis of RCTs of folic acid supplementation

A meta-analysis of RCTs of folic acid supplementation (Vollset et al. 2013, http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)62001-7/abstract) tested whether relatively high levels of folic acid consumption cause or prevent cancer overall, and found a marginally statistically insignificant 6% increase in cancer incidence among participants taking folic acid supplements. Although the authors of the meta-analysis interpreted the results as evidence that folic acid consumption does not affect cancer risk in the short term, there are justifications for a more cautious interpretation:

- The hypothesis tested in the meta-analysis was whether folic acid supplementation caused or prevented cancer overall. If there is a dual relationship between folic acid and cancer, however, folic acid may have promoted cancer growth and detection in some individuals with previously initiated cancer, and prevented the initiation of

cancer in others, which could superficially appear as though there is little or no effect. Since the overall increase in cancer rates was relatively small and statistically insignificant, the results of the meta-analysis do not raise large concerns at a population level. It may not be appropriate for individuals with early stage cancer, however, to believe that consuming excess folic acid has no effect on cancer progression.

- The authors of the meta-analysis note that the median dosage of folic acid supplements in the randomized controlled trials is an order of magnitude higher than the daily amount expected to be consumed in a country with mandatory folic acid food fortification. However, in countries with folic acid food fortification, it appears that a large proportion of the population's folic acid intake is in excess of their bodies' capacity to metabolize it, since unmetabolized folic acid can be observed in blood and observed accumulating in cells. We do not know whether having unmetabolized folic acid in the blood and in cells is harmful, but some worry that it is.
- The characteristics of the participants in different RCTs included in the meta-analysis may be varied, which makes it difficult to generalize the results to entire populations consuming folic acid in supplements or fortified foods. Participants in one RCT may have had a large number of initiated but not yet clinically evident cancers at the start of a trial (which could lead to an increase in detected cancer incidence in the treatment group in the trial), while another RCT's participants might have had none.

Overall, Dr. Miller is cautiously optimistic that, at the population level, folic acid fortification does not increase cancer risk on net. A major reason for his optimism is that the RCTs on folic acid supplementation and cancer risk provided a much larger dosage of folic acid than a typical member of the population would receive under fortification.

Implications for folic acid food fortification programs

When considering folic acid food fortification, it is ethically difficult to weigh a highly certain aversion of a few thousand neural tube defects per year against potentially exposing millions of people to excess folic acid since it is plausible, but highly uncertain, that excess folic acid could cause harm to those with initiated cancers. There may be a fortification level that balances risks and benefits by providing enough folic acid to prevent neural tube defects, but not enough to exceed a large proportion of the population's capacity to metabolize folic acid.

Before mandating folic acid food fortification, national governments should consider the number of pregnancies per year expected to be affected by neural tube defects, the population's current folate status, the number of people expected to be exposed to excess folic acid, and the feasibility of fortification. In countries that already have low numbers of neural tube defects and good folate status, such as Finland, the risks of folic acid

fortification may outweigh the benefits. In other countries, the case for fortification may depend on logistical feasibility; for example, populations in northern China have low folate status and a high rate of neural tube defects, but the staple food is rice, which is more costly and difficult to fortify than flour. Finally, there are options other than mandatory fortification: for example, in the United Kingdom, folic acid fortification is voluntary but not mandated, which may improve folate status without exposing too many people to excess folic acid.

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