BMJ

BMJ 2012;344:e1662 doi: 10.1136/bmj.e1662 (Published 12 March 2012)

EDITORIALS

A reduced risk of Alzheimer's disease in those who survive cancer

Cold comfort for individual patients?

Mary Ganguli *professor of psychiatry, neurology, and epidemiology*

University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

In a linked population based cohort study (doi:10.1136/bmj.e1442), Driver and colleagues report that older adults who survived cancer had a lower risk of developing Alzheimer's disease than those who had never had cancer. Furthermore, people with Alzheimer's disease had a lower risk of subsequent cancer than those without the disease.[1] This report of an apparent mutually protective relation between Alzheimer's disease and cancer is intriguing although not unprecedented. Others have previously hinted at such a link,[2-4] and a similar pattern has been described for cancer and Parkinson's disease.[5] So, are neurodegeneration and cancer inversely associated? Should doctors tell their patients with newly diagnosed cancer that they have a reduced risk of Alzheimer's disease (or vice versa)?

Epidemiologists dream of discovering new risk (or protective) factors for disease. However, the path of analytical epidemiology is littered with observational findings that briefly made headlines but then failed to be replicated by other observational studies, or to be borne out by experimental studies. We should search diligently for alternative explanations for new observed associations because the inevitable backlash against results that are not confirmed by other studies tends to deepen scepticism about epidemiological research.[6]

Hazard ratios compare the hazard of disease in people who are exposed to the so called risk factor to the hazard of disease in unexposed people over a given period. The observed association provides a signal with varying signal to noise ratio. Although a factor might be statistically associated with an increased (or reduced) probability of developing disease, it might not be part of the causal pathway for that disease; instead it might mediate or modify the effect of another factor, it may be a confounder, or it might merely be associated through inadvertent bias.[7]

Driver and colleagues rightly consider the phenomenon of survival bias.[8] Is it possible that the observed negative association is not between cancer and neurodegeneration but rather between survival from cancer and neurodegeneration? Would people who died from cancer have developed dementia if they had lived long enough? If so, their removal from the pool could result in the spurious finding that cancer survivors have a reduced statistical probability of dementia.

Readers should also consider the possibility that a third factor associated with both cancer and neurodegeneration is the real protective factor. The current study found that the risk of Alzheimer's disease was especially low in survivors of smoking related cancers.[1] Smoking reduces life expectancy and is a well established risk factor for several cancers. The association between smoking and Alzheimer's disease is less clear. Cross sectional studies have shown a negative (potentially protective) association between smoking and Alzheimer's disease, which has been confirmed by some longitudinal studies but directly contradicted by others. A biologically plausible explanation is available for both observations. However, the phenomenon known as competing risk allows another explanation[9 10]—that patients who died from smoking related cancers may have developed smoking related Alzheimer's disease had they lived long enough.

Statistical mechanisms used to adjust for these biases typically assume that the incidence of Alzheimer's disease would have been the same in those who died as in those who survived or make some other assumption to model competing risks. However, it currently is not possible to know the underlying distribution of incipient cancer, or incipient neurodegeneration, in those who do not survive long enough to develop the disease in question.

Cancer may also have been under-ascertained in this cohort because slow growing tumours had not become symptomatic or were not actively screened for, the detection of asymptomatic cancer not being part of the study. Survivors of cancer may be exceptionally hardy and able to resist for longer the ravages of neurodegeneration.

Is it impossible then to know whether surviving cancer truly protects against neurodegenerative disease in a population? It is hard to imagine a better population "laboratory" than the Framingham Study, which closely evaluates and monitors a large community based cohort over time, thereby minimising selection bias and recall bias. However, all potential biases and confounding effects cannot be accounted for in an observational study. The most promising approach to settling the matter might be so called life course epidemiology.[11] If reliable biomarkers

gangulim@upmc.edu

were available for both cancer and Alzheimer's disease, and all participants could be repeatedly screened for both diseases from early adulthood, the true associations and temporal sequences could be determined with greater accuracy.

Assuming the associations seen in the current study are true, is there a plausible mechanism to explain a protective effect of cancer survival on Alzheimer's disease? The authors suggest that a biological mechanism common to both cancer and neurodegenerative disease may be inappropriate activation and regulation of the cell cycle, with uncontrolled proliferation underpinning one disease, and apoptosis (at the opposite end of the spectrum) driving the other. Other possibilities have also been proposed.[9] Recent findings from an experimental study suggested that the cancer chemotherapy drug bexarotene reduced build-up of amyloid in the brains of mice bred as models for human Alzheimer's disease.[12] This hypothesis requires further testing and may bring new understanding of the mechanisms of both diseases.

In the future, personalised medicine may allow risk profiles for cancer or neurodegeneration to be identified, allowing people to tailor their lifestyles according to genetic risk. If so, we may well look back and salute the epidemiologists who first spotted the connection reported here. Currently, however, patients who receive a new diagnosis of Alzheimer's disease or cancer will probably draw cold comfort from their reduced probability of developing the other disease if they live long enough. The message for them is that these results have no immediate implication at the individual level, but that they do offer some hope that new insights into disease mechanisms will lead to improved prospects for prevention and treatment.

Competing interests: The author has completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: partial support from grants R01AG023651 and K24AG022035 from the National Institute on Aging, National Institutes of Health, US Department of Health and Human Services; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; not externally peer reviewed.

1 Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, et al. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. *BMJ* 2012;344:e1442.
2 Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC. Alzheimer disease and cancer. *Neurology* 2005;64:895-8.
3 Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, et al. Cancer linked to Alzheimer disease but not vascular dementia. *Neurology* 2010;74:106-12.
4 Yamada M, Sasaki H, Mimori Y, Kasagi F, Sudoh S, Ikeda J, et al. Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Radiation Effects Research Foundation. *J Am Geriatr Soc* 1999;47:189-95.
5 Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes Control* 2010;21:697-707.
6 Johnston SC, Hauser SL. The challenge of publishing newsworthy epidemiology. *Ann Neurol* 2010;67:A8-10.
7 Ganguli M, Kukull WA. Lost in translation: epidemiology, risk, and Alzheimer's disease. Arch Neurol 2010;67:107-11.
8 Kukull WA, Ganguli M. Generalizability: the trees, the forest, and the low-hanging fruit. *Neurology* (forthcoming).
9 Bennett DA, Leurgans S. Is there a link between cancer and Alzheimer's disease? *Neurology* 2010;4:100-1.
10 Chang CC, Zhao Y, Lee CW, Ganguli M. Smoking, death, and Alzheimer disease: a case of competing risks. *Alzheimer Dis Assoc Disord* 2011; published online 17 December.
11 Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol* 2006;5:87-96.
12 Cramer PE, Cirrito JR, Wesson DW, Lee CY, Karlo JC, Zinn AE, et al. ApoE-directed therapeutics rapidly clear beta-amyloid and reverse deficits in AD mouse models. *Science* 2012; published online 9 February.

Cite this as: *BMJ* 2012;344:e1662