The ABC breast cancer cluster: the bad news about a good outcome

Michael D Coory

To the Editor: An editorial by Stewart alludes to the problem of silent multiple comparisons when interpreting *P* values from cancer cluster investigations.[1] Visible multiplicities such as occur with pre-specified subgroup analyses or sequential monitoring of trials are difficult enough, but at least in these circumstances we know how many multiple comparisons are under consideration. More difficult are silent multiplicities such as occur with cluster investigations (and also with publication bias[2] or reporting bias[3]) where we do not know how many multiple comparisons should be considered.

The *P* value is intended to be an objective measure of the play of chance, and this is (arguably) the case when applied to a pre-specified primary hypothesis in a randomised trial. But this is not the case for cluster investigations, in which the number of multiple comparisons can never be known with any certainty. Statisticians analysing data from a cluster could obtain any *P* value they wanted by calibrating it against an arbitrary number of multiple comparisons.

Where does this leave scientific reasoning in cluster investigations? All cases of cancer have causes; the key question in a cluster investigation is whether the cases have a common cause related to the neighbourhood or workplace from which the cluster was reported. Only rarely is an obvious common cause identified, and a decision to take some action (eg, evacuate the workplace) needs to be based on expert opinion.

For the ABC cluster, no obvious common cause was identified. However, the expert

panel was concerned that the women with breast cancer were relatively young and were long-term employees at the site, suggesting that there might be an unidentified common cause related to the site.[4] This concern, based on expert opinion, is (arguably) enough evidence to evacuate the site.

Investigation of cancer clusters is a difficult task. If a common cause cannot be identified, then there is no objective evidence on which to obtain agreement among experts about the importance of the cluster. Specifically, we need to be very clear that, for cluster investigations, a *P* value (even when adjusted for multiple comparisons) does not provide an objective measure of whether the cluster is due to chance. In the end, an expert group has to make a decision in the presence of uncertainty. When communicating the results to the public, the uncertainty should be acknowledged — as should the fact that experts sometimes disagree.

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To the Editor: We read with interest the report by Sitas and colleagues about the Australian Broadcasting Corporation (ABC) breast cancer cluster investigation.[1] After publication of the final report on the ABC cancer cluster,[2] the Public Health Unit of Sydney South West Area Health Service undertook a similar investigation.

In May 2007, our Public Health Unit was contacted by an occupational health representative after reports of five recent cases of breast cancer among women working in two departments at a Sydney hospital between 2002 and 2006. Four of these cases were confirmed, and all four women had offices in the same area of the hospital. Based on the assumption that women employed in these two departments between 2001 and 2006 (a total of 69 women) were the population "at risk", we found that there was an excess of observed cases over expected cases (standardised incidence ratio [SIR], 15.1 [95% CI, 4.1–38.8]; $P < 0.001$).

There were no known hazards affecting these women that would not be present elsewhere in the hospital, so an expert panel recommended a hospital-wide epidemiological investigation and environmental survey. The case definition was any woman diagnosed with invasive breast cancer while working at the hospital between 1 January 1998 and 31 August 2007. To ascertain cases, we wrote a letter to all current employees and issued a media release.

A dedicated telephone hotline received 147 calls from 19 July to 31 August 2007. We confirmed 24 cases meeting the case definition. These women had a mean age of 51 years at diagnosis, had worked at the hospital for a median of 11 years, were not clustered by work location or type, and had similar risk factors for developing breast cancer to women in the New South Wales population as a whole.

From employment records and NSW cancer statistics, we calculated that 23 cases of invasive breast cancer would be expected based on the age structure and size of the female workforce at the hospital over the study period. The observed number of cases was not significantly different from the expected number (SIR, 1.1 [95% CI, 0.7–1.6]; $P = 0.44$).[3] In the environmental survey, no unusual hazards were identified.

Breast cancer is the most common invasive cancer diagnosed in Australian women.[4] In most cases, potential "clusters" are probably a chance occurrence, even when the number of cases is statistically significantly higher than expected, with no plausible explanation identified.[5] Our investigation found no excess of cases of breast cancer in women employed at the hospital over the study period.

Guidelines[6] are helpful in defining a consistent approach to cluster investigation, but such investigations are resource intensive. Careful initial analysis of information is important to determine whether further investigation of a reported cluster is warranted. In our study, we concluded that a broader investigation was justified.

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