Commentary: Antidepressants and breast cancer risk

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Animal studies indicate that neonatal exposure to antidepressants may induce or stimulate mammary tumour growth, and may enhance carcinogenesis in the colons of rats, and therefore might generally represent hazards for cancer in man. Hence the search for a role for antidepressants in breast cancer in human studies, for example, will no doubt continue. Meanwhile these studies may cause alarm. A paper from Ontario in this issue of the International Journal of Epidemiology continues this search—arguing for a small increase in risk—based on a large case-control study. The authors state that since breast carcinogenesis is a complex multistage process it is likely that the effects of exposure to antidepressants, if any, would be difficult to detect above the background of other exposure and susceptibilities.

Possibly, but maybe there really is no general causative association.

Clearly it is not possible to be at all certain about this relationship, and certainly not to recommend any change in the use
of antidepressants on account of putative breast cancer risk. The relationship is far too insecure and possibly complex. But it certainly cannot be excluded as a possible small hazard, estimated here as a 20% increase in risk.

In this case confounding is not the explanation, according to these authors, although that is by no means certain. A cohort study published in 2001 of 75,000 women noted several associations with antidepressant use that could confound any comparison, whether measured or not. In that study, the cohort of antidepressant users, compared with non-users, were more likely to be white, to have used oestrogen in the past, to have had benign breast disease, to have a history of alcohol misuse, and so on. The main risk factors of family history, menstruation, childbirth, and breastfeeding were not recorded, nor adjusted for in these analyses. But the incidence of breast cancer was nonetheless essentially identical between users and non-users. Other studies cited by these authors have shown apparent protective effects of antidepressants too. But where do we go from here?

This problem of course is not new. We already have alcohol as a possible risk factor and certainly hormone replacement therapy. Along with antidepressants, all three clearly have their place in the general business of enabling women to feel better, by means of their choosing. None is going to vanish, nor even importantly decrease, on grounds of possible attributable increases in breast cancer incidence. It is an enduring problem for women wishing to avoid breast cancer, with small possible risks of varying epidemiological validity. In the case of antidepressants the validity is the weakest of the three.

So we have to look at possible mechanisms—change in susceptibility, carcinogenesis, stimulation of existing cancer, or gene interactions for example—for the association, possibly for specific antidepressants only, to have meaning for future research. Sadly, case-control studies of the kind that tend to investigate this association are merely fishing expeditions. In this case the overall ‘increase’ is not supported by any ancillary findings to do, for example, with duration of use or time since use. But one would not expect anything but a very strong effect to show in such a study. So, in the end, all possible mechanisms are being simultaneously tested—with little precision. An overall odds ratio of marginal significance is all that can be expected, with occasional vague (and possibly misleading) pointers to plausible mechanisms. But these will generally be impossible to distinguish from random noise and may well provoke more wild goose chases.

A far better approach from now on would be to decide a priori on the most plausible mechanism for particular antidepressants, and simply to test particular possibilities with more rigour (rather than testing them all), beginning with the study design and ending with the report. Steingart et al. suggest a honing down of the hypotheses to possible particular neuroendocrine consequences, or the effects of antidepressants on possibly benign proliferative breast disease or on breast density. Further epidemiological fishing expeditions are only going to confuse. Marginally significant odds ratios of around 1.2 are ubiquitous in this disease, and the fact that breast cancer is common does not, of itself, make these risks any more real—just more worrying. But an epidemiological effect that has plausible scientific meaning can be very helpful in reducing the risk of this disease. If there is any effect, it is incumbent upon epidemiology to discern it—largely by jettisoning fishing expeditions and concentrating on plausible and testable effects. In the end, unknown confounding will remain the greatest problem for anything but large and clear effect sizes.

References