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Regional Block and Cancer Recurrence: Too Early to Tell

To the Editor:—We read with much interest the recently published study by Exadaktylos *et al.*[1] Their retrospective cohort study identified a beneficial relation between paravertebral block and cancer recurrence in women undergoing breast cancer surgery. The authors opined that regional anesthesia might help to maintain normal perioperative immune function and reduce the risk of tumor recurrence and metastases. If these findings are real, it would be the first demonstration that anesthesia *per se* protects from cancer recurrence—a true revolution.

However, before such conclusions can be drawn, a number of limitations of this study should be addressed. Although some were discussed in the excellent accompanying editorial by Ochroch *et al.*,[2] some major ones seem to have gone unnoticed.

First, the authors state that prognostic factors and particularly the Nottingham Prognostic Score were similar in both groups. As a consequence, the smaller number of cancer recurrence and metastases observed in the paravertebral group seems to be due to the inherent benefits of the regional technique. However, the Nottingham Prognostic Score is not a measure of the propensity for tumor recurrence or metastasis.[3] It has never been validated as such. Only axillary node extension and histologic grade of the tumor have been demonstrated to do this. There is evidence from the literature suggesting that patients with high-grade (grade III) histologic breast tumors undergoing surgery are more at risk of recurrence and metastasis than patients with lower grades.[4,5] Reanalyzing the study data of Exadaktylos *et al.*,[1] it seems that 54% of patients in the nonblock group compared with 42% of patients in the paravertebral block group had high-grade breast tumors and increased risk of cancer recurrence. Had categorical variables from the histologic grades been compared as is recommended,[6] with the chi-square test (and not the Mann–Whitney U test for nonnormally distributed numerical variables), it would have been found that patients in the nonblock group had poorer prognosis at a P value less than 0.001.

Second, the authors assume a cause–effect phenomenon between the predictor (the anesthetic technique) and the outcome (cancer recurrence or metastasis). However, the opposite may be true here: The outcome may have caused the predictor to occur. Treatment allocation seemed to be mainly influenced by the anesthesiologist's decision to use a paravertebral block. A block may not have been offered to patients in whom it was not indicated (*e.g.*, patients with extensive metastases, recurrent or bilateral breast tumors).[7] As a consequence, patients with extensive, recurring, or bilateral tumors were less likely to have a paravertebral block. Cancer recurrence might have guided the choice of the anesthetic technique and not the opposite. This effect–cause phenomenon is recognized bias of cross-sectional, case–control, and retrospective cohort studies.[8] There are some well-known examples in the literature, such as the protective effect of tobacco smoking against Parkinson disease or the deleterious effect of low levels of blood cholesterol in cancer patients.[9,10] In both cases, presumed consequences (Parkinson disease–cancer) are actually causes of lower tobacco smoking and blood cholesterol.

Finally, in the study of Exadaktylos *et al.*,[1] paravertebral blocks were performed by the same anesthesiologist, and all such cases were performed by the same surgeon and managed by the same oncologist. What about the "nonblock" cases? Were the latter patients managed by a range of surgeons and oncologists, perhaps with different approaches to treatment? There may be other explanations as to why the latter patients had poorer outcomes.[11]

In conclusion, the only study design able to reliably answer whether paravertebral block really protects from breast cancer recurrence is a randomized controlled trial. This should be done as soon as possible before an unproven hypothesis becomes a standard of practice in breast cancer surgery.

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In Reply:—We thank Drs. Haller and Myles for their comments regarding our article.[1] They suggest that a reanalysis comparing our paravertebral and general anesthesia groups treating histologic grade as a categorical factor shows the groups to differ on histologic grade, thus implying an overlooked problem with confounding.

This is simply not the case: A chi-square analysis comparing the groups on histologic grade III *versus* the combined I/II, as suggested, leads to a P value of 0.19 (not the < 0.001 stated by Haller and Myles). This is less significant than the $P = 0.16$ that we reported when considering the variable to be ordinal. The primary reason is that there is a loss of information on histologic grade by collapsing the first and second levels, which is why we analyzed all three categories. Furthermore, our analysis using the Mann–Whitney test is a more powerful way to detect group differences on severity because it uses the natural ordering, as opposed to simply considering the grades as nominal categories such as red, white, and blue, as the chi-square test does.

Most importantly, adjustment for histologic grade in our multivariable analyses of cancer recurrence obviates concern for the potential con-