

A gene-expression profile independently predicted disease outcome in young women with breast cancer

van de Vijver MJ, He YD, van't Veer LJ, et al. A gene-expression signature as a predictor of survival in breast cancer. *N Engl J Med.* 2002;347:1999-2009.

QUESTION

In young women with breast cancer, what is the prognostic value of a gene-expression profile for predicting disease outcome?

DESIGN

Analysis of tumors from a consecutive series of patients selected from a fresh-frozen tissue bank to evaluate a previously established gene-expression profile.

SETTING

The Netherlands.

PATIENTS

295 women with primary invasive breast carcinoma < 5 cm in diameter at pathological examination. Other inclusion criteria included age \leq 52 years at diagnosis, tumor-negative apical axillary lymph nodes, and no history of cancer (except nonmelanoma skin cancer). Among the 295 women, 151 were lymph node-negative and 144 were lymph node-positive. All patients had been treated by modified radical mastectomy or breast-conserving surgery, and subsequent radiotherapy if indicated.

DESCRIPTION OF PREDICTION GUIDE

61 patients with lymph node-negative disease were involved in a previous study that established a 70-gene prognosis profile. Using micro-array analysis, the 234 tumors from patients not included in the previous study were each used to calculate the correlation coefficient of the level of expression of the 70 genes with the previously determined mean profile of these genes in tumors from patients with a good prognosis. A patient with a correlation coefficient of > 0.4 was classified as having a good prognosis gene-expression signature; all other patients were classified as having a poor prognosis gene-expression signature. For the 61 patients included in the previous study, a cutpoint of 0.55 was used.

MAIN OUTCOME MEASURES

Survival and risk for distant metastases.

MAIN RESULTS

Of the 295 patients, 180 had a poor prognosis signature and 115 had a good prognosis signature. The mean overall 10-year

survival rate was 54.6% for patients with a poor prognosis signature and 94.5% for patients with a good prognosis signature. At 10 years, the probability of remaining free of distant metastases was 50.6% for patients with a poor prognosis signature and 85.2% for patients with a good prognosis signature. The multivariate proportional-hazards ratio for risk for distant metastases as a first event in the group with a poor prognosis signature (vs the group with a good prognosis signature) was 4.6 (95% CI 2.3 to 9.2, $P < 0.001$).

CONCLUSION

In young women with breast cancer, a gene-expression profile independently predicted outcome of disease.

Source of funding: The Netherlands Cancer Institute.

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COMMENTARY

The study by Van de Vijver and colleagues reports that a micro-array analysis of genetic patterns from women with primary breast cancer was able to identify a "fingerprint" of which cancers had a good or bad prognosis. This study provides evidence of the potential prognostic value of genetic analysis. In addition, it should prompt cancer biologists to question or reformulate their multistep tumor genesis models. However, such analyses are not yet ready for routine use in clinical practice.

Several limitations of this study are worth emphasizing. This was a retrospective study of 295 patients, of whom 61 were included in an earlier preliminary study. Although patients were consecutive, the sample size seems to have been one of "convenience" (1). The technical feasibility and time needed to do the micro-arrays are not discussed.

Still, the primary findings are compelling for the sample size used. This study was able to stratify groups with a poor and good prognosis and to identify patients having low risk in the node-positive subgroup. The latter may be clinically important because almost all of these patients receive some form of adjuvant therapy at the present time.

Just because a prediction model can be developed to identify *prognostic* factors does not necessarily mean that they are *predictive* factors of treatment response. Presently in breast cancer, only estrogen-receptor

status and human epidermal receptor-2 (HER-2) are clinically useful predictive factors. However, no known predictive factors exist for women with estrogen-receptor negative and HER-2 negative breast cancer. In this regard, the study suggests that gene-expression signature may be able to make important *prognostic* distinctions for node-negative patients. Studies are now needed to determine if a benefit of adjuvant chemotherapy, expressed as a relative risk reduction in cancer recurrence, is constant in women with genetically stratified cancer. Lastly, the micro-array technology involves thousands of genes, raising concerns of false-positive results (1). I eagerly await the first report from an independent group validating these results in a separate breast cancer cohort.

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Reference

1. Webb T. Microarray studies challenge theories of metastasis. *J Natl Cancer Inst.* 2003;95:350-1.