We appreciate the opportunity to comment on the article entitled “Interaction Between Breast Cancer Cells and Adipose Tissue Cells Derived from Fat Grafting” by Massa et al. The authors investigated a controversial topic that has polarized plastic surgeons for many years, namely the role of fat grafting in carcinogenesis. In a common in vitro model, undigested adipose tissue, cells of the stromal vascular fraction (SVF) with or without induction of adipogenic differentiation, were cocultured with three different breast-cancer cell lines in a Boyden chamber. Bone-marrow-derived stroma cells served as a control. The results show that the proliferation of all three cancer cell lines was induced by whole adipose tissue, in vitro differentiated adipocytes, and, to a lesser extent, non-induced SVF cells.

The present study represents an effort to shed light into the pathomechanisms of adipose tissue-fueled cancer development. We have recently shown that adipose tissue not only promotes breast cancer but also other cancer entities such as melanoma in a comparable experimental setting. It is a feasible approach to compare the cancer-proliferative character of adipose tissue, differentiated adipocytes, and SVF cells and to compare them to a nonadipogenic control. Although the present study certainly enriches our knowledge of the carcinogenicity of fat, we want to address one major concern in the ongoing debate of fat grafting and carcinogenicity. The authors correctly state: “from a clinical point of view, the oncological role of the transplanted adipose tissue in promoting local recurrence has not yet been clarified.” A great number of in vitro studies and animal experiments have provided an undeniably strong body of evidence for a potential carcinogenic effect of whole adipose tissue, adipocytes, and SVF cells including adipocyte-derived stem cells (ASC). These observations have naturally led to uncertainty and a sensitization of our perception towards fat grafting, which gained respectable popularity as an almost omnipotent tool in plastic surgery. However, the uncertainties are perpetuated by the fact that in the midst of the accumulation of convincing experimental evidence, clinical data largely do not confirm an increased risk of carcinogenicity, metastatic spread, and recurrence in patients after autologous fat grafting. The question of the missing link between experimental and clinical studies remains unanswered.

One decisive reason for the discrepancies is found in the experimental design. Most experimental studies so far focused on the proliferation of different cancer cells, mostly breast-cancer cell lines, when cocultured or co-injected with adipose tissue or cells fractioned from adipose tissue. Although the majority of these types of studies surely reveal an important finding (that adipose tissue and its cell fractions in fact facilitate tumor growth), their informative value regarding tumor progression via fat grafting appears to be limited. Cancer cells are embedded in tumor stroma, which in the case of breast cancer, in particular, predominantly consists of adipose tissue. Therefore, showing a tumor proliferative effect of adipose tissue on cancer cells does not specifically address the problem of fat grafting on...
cancer development. It merely shows the effect of adipose tissue including physiological tumor stroma on carcinogenesis, but not a carcinogenic risk of the fat grafting procedure per se.

At this point in the research, an extension of experimental approaches is of pivotal importance. Apart from exploration of mechanisms in obesity and tumor-stroma-related carcinogenesis, which are, in all respects, relevant topics in the broad field of cancer research, the main focus of plastic surgeons lies in the concrete investigation of fat grafting on cancer development. What is the rationale to hypothesize that adipose tissue transferred from one part of the body to the other induces cancer and cancer recurrence when the cancer cells are embedded in fat tissue to begin with? Do lipoaspirates differ from the adipose tissue that naturally surrounds the local cancer cells caused by the manipulation lipoaspirates undergo during the harvest, processing, and injection steps?

Furthermore, more intense efforts are desirable to unravel underlying mechanisms in carcinogenesis, find new potential therapy targets, and encourage translational strategies for the future. For instance, Eterno et al have identified c-Met, also known as hepatocyte growth factor receptor (HGFR), as a marker to predict the risk of breast-cancer recurrence for patients with utmost caution and perform a careful follow-up. Until a scientifically sound, comprehensive consensus is reached, we agree with the authors to select patients with utmost caution and perform a careful follow-up.

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REFERENCES