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Letter to the Editor

Cardenolides and cancer

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I read with great interest the article by Pathak *et al*.[1] It is somewhat puzzling that studies like the one described by the authors are not performed to a much larger extent, in particular since there are strong indications that cardiac glycosides (both digoxin and digitoxin in cardiotherapeutic concentrations) influence a number of functions of human cancer cells even in a clinical situation. We reported that the tumor cell populations from breast cancer patients on digitalis medication (for cardiac problems) were characterized by a number of cytometric features,[2,3] which strongly indicated that they had a lower proliferative capacity than tumor cells from patients not on digitalis treatment. Moreover, the patients on digitalis had breast cancers which were approximately half the size[3] of those not in digitalis. We reported also after 5-year follow-up that the recurrence rate among patients not on digitalis was 9.6 times (confidence interval 1.2–35.8) higher than among patients on digitalis.[4] In a 20-year follow-up I have recently reported[5] that the death rate from breast carcinoma (excluding other causes of death and confounding factors) was 6% (two of 32) among patients on digitalis, compared with 34% (48 of 143) among patients not on digitalis (p=0.002). The low number of patients of course required caution with the interpretation, but should have triggered other independent research activity.

However, recently, it has been shown that both digitoxin and dixoxin have growth inhibitory effects on both receptor-positive and receptor-negative human breast cancer cell lines *in vitro*, and inhibited proliferation and induced apoptotic cell death in two of three human-derived hematological cell lines.[6] It has also been shown that digitalis sensitized malignant breast tumor cancer cells for radiation *in vitro*, seemingly because digitalis blocks the tumor cells in the G_2/M phase.[7] Some of the inhibitory effects of digitalis on proliferating cells is likely to be achieved by its Na/K-ATPase inhibition. Recently, it has also been shown that digitoxin inhibits in tissue culture cells from human glioblastomas.[8] This is interesting also from the point that digitalis crosses the blood–brain barrier.

The above-mentioned observations call for larger controlled studies of cardenolides/digitalis and death from breast cancer and, as it seems, also some other cancers (excluding other causes of death). Among a number of questions, it also remains to clarify what influence digitalis derivatives have on angiogenesis and dyscohesion of cancer cells. Such studies are not too expensive to perform and could consist of both experimental (*in vivo* and *in vitro*) and epidemiological investigations as well as randomized clinical trials with digitalis as an additional adjuvant therapy considering the comparatively well-known pharmacology of digitalis.

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