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Comment on: α-smooth muscle actin expression and desmoplastic stromal reaction in pancreatic cancer: results from the CONKO-001 study

I H Sahin*[,1] and B Uzunparmak[2]

[1]Department of Medicine, Mount Sinai Icahn School of Medicine, St Luke's Roosevelt Hospital Center, New York, NY, USA and [2]Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Sir,

We read with great interest the recent study by Sinn *et al* (2014) that demonstrated significantly increased α-smooth muscle actin (α-SMA) expression in pancreatic cancer stroma, which was correlated with worse survival outcomes in patients who underwent tumour resection and did not receive any adjuvant treatment. The authors also showed that dense stroma in the tumour microenvironment is associated with better outcomes in pancreatic cancer patients. We would like to discuss further points about the relationship between increased α-SMA expression and worse outcomes in pancreatic cancer patients.

Increased Sonic Hedgehog signalling in both tumour cell and tumour stroma has been found to be related to increased α-SMA expression (Bailey *et al*, 2008). Sonic Hedgehog signalling has also been demonstrated to be involved in pancreatic cancer stem cell development (Takebe *et al*, 2010), and the Sonic Hedgehog transcript was shown to be increased four-fold in the general pancreatic cancer cell population, but 46-fold in CD44 + CD24 + ESA + pancreatic cancer stem cells (Lee *et al*, 2008). Moreover, pancreatic cancer stem cells have a 100-fold greater tumour-initiating capability compared with non-stem pancreatic cancer cells (Li *et al*, 2007). Therefore, increased α-SMA expression actually may indirectly indicate an increased pancreatic cancer stem cell population that is directly related to tumour growth and metastatic activity (Hermann *et al*, 2007), and the associated increased Sonic Hedgehog signalling in the tumour microenvironment.

A recent study showed that stromal elements that respond to tumour growth restrain the tumour growth, and that inhibition of the stromal response induces more aggressive tumour behaviour and disease progression via increased angiogenesis (Rhim *et al*, 2014). Similarly, increased cell proliferation in pancreatic intraepithelial neoplasia has been observed upon inhibition of hedgehog signalling in the tumour stroma (Lee *et al*, 2014). Moreover, a phase II clinical trial investigating the role of the Sonic Hedgehog signal inhibitor, saridegib combined with gemcitabine, was terminated early due to worse survival outcomes in the treatment arm compared with the placebo plus gemcitabine arm (Lou, 2014). A more recent clinical trial also failed to demonstrate any benefit of inhibiting the Sonic Hedgehog pathway; even more strikingly, there was no significant effect on pancreatic cancer stem cells either (Kim *et al*, 2014).

Altogether, elevated α-SMA expression in tumours may be indirectly related to survival outcomes and rather it may be a sign of increased cancer stem cell population, as studies have shown no benefit upon inhibition of desmoplasia. Further studies are required to enlighten the exact relationship between cancer stem cells and the tumour microenvironment.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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*Correspondence: Dr IH Sahin; E-mail: md.ibrahim.halil.sahin@gmail.com
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Sleep duration and breast cancer risk in the breast cancer detection demonstration project follow-up cohort: true associations or bias?

W-S Yang*[,1,2], X Wang[1,2], Q Deng[1,2], H Zhao[1,2] and W-Y Fan[1,2]

[1]Department of Social Science and Public Health, School of Basic Medical Science, Jiujiang University, No. 17, Lufeng Road, Jiujiang 332000, China and [2]Jiangxi Province Key Laboratory of Systems Biomedicine, Jiujiang University, No. 17, Lufeng Road, Jiujiang 332000, China

Sir,

We read with interest the recent publication by Qian *et al* (2014). The authors examined the risk of incident breast cancer (BC) associated with sleep duration using data from Breast Cancer Detection Demonstration Project follow-up cohort, and found a null association between sleep hours and overall BC. They also reported risk estimates for BC according to different molecular subtypes of BC, and suggested a decreased risk for estrogen receptor (ER) + progesterone receptor (PR) + BC with shorter sleep duration. The information provided is of interest as the relationship between sleep and BC is of increasing concern. However, we would like to raise several concerns related to this paper.

First, the validity of the sleep questionnaire used in the study is unclear. As self-reported sleep duration is potentially subject to misclassification, and the exposure variable (sleep hours) was categorical, even random misclassification may have led to bias in any direction (Rothman *et al*, 2013). A previous validation study (Girschik *et al*, 2012) concluded that a three-item sleep questionnaire that is similar to one used in the study by Qian *et al* (2014) and typically employed in other epidemiologic sleep studies exhibited a poor agreement with objective measures of sleep as assessed using actigraphy (kappa coefficients ranging from −0.19 to 0.14). Thus, the misclassification bias for exposure data in their study cannot be ruled out. Moreover, the data on sleeping habits in