

# Insulin-like growth factor-1 enhances mortality risk in women with breast cancer through epithelial-mesenchymal transition initiation

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## ABSTRACT

The metastatic disease which leads to cancer patients' mortality results from a multi-step process of tumor progression caused by gene alteration and cooperation. Accordingly, it was recently demonstrated that alteration level of insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) are associated with the risk of cancer related death in several human malignancies including breast cancer. On the other hand, epithelial-mesenchymal transition (EMT) is described as a crucial event in cancer progression and metastasis. Herein, we discuss the association between IGF-1, IGF-1/IGFBP-3 ratio, EMT, and breast cancer mortality.

**Key words:** Breast cancer, cancer mortality, EMT, IGF-1, IGFBP-3, metastasis

Cancer metastasis, one of the hallmarks of malignancy, is the primary cause of death in breast cancer patients. Cancer cells can detach from a primary tumor and circulate through the vascular or lymphatic system and settle down to launch a secondary tumor within normal tissues elsewhere in cancer patients. This process is governed by several genes and/or oncogenes interactions. Meanwhile, it is established that Insulin-like growth factors (IGFs) can activate pro-survival and anti-apoptotic intracellular signaling networks and therefore are considered to play an important role in cancer development and metastasis.<sup>[1]</sup> In this context, a very interesting recent study revealed that there is a strong association between circulating IGF-1 and the main binding protein, IGFBP-3, and breast cancer mortality in cancer patients.<sup>[2]</sup> The authors of this investigation examined the association between levels of circulating IGF-1 and IGFBP-3 with risk of breast cancer and all-cause mortality using Cox proportional

hazards models in a cohort of 600 women diagnosed with breast cancer. They showed that high levels of IGF-1 are associated with risk of all-cause, but not with breast cancer-specific mortality in this cohort of cancer patients. Meanwhile, they demonstrated that the IGF-1/IGFBP-3 ratio, which is an indicator of IGF-1 levels and consequently the activation of its receptor, is significantly associated with increasing risk of all-cause mortality in these breast cancer patients. Therefore, they concluded that high levels of IGF-1 and IGF-1/IGFBP-3 ratio are associated with increased risk of all-cause mortality in women with breast cancer. Finally, the authors claimed that their results need to be confirmed in large cohorts of breast cancer survivors to determine the significance of this association, which we believe is an important and worthy goal.

On the other hand, the epithelial-mesenchymal transition (EMT) describes the de-differentiation switch between polarized epithelial cancer cells and contractile and mesenchymal (invasive) cells during cancer progression and metastasis.<sup>[3]</sup> Numerous studies including ours have shown a high correlation between loss of E-cadherin and their associated proteins, catenins, the gain of vimentin and fibronectin and cancer invasiveness in cancer cells.<sup>[3,4]</sup> Meanwhile, accumulating evidence suggests that receptor tyrosine kinases (RTKs), such as epithelial

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growth factor-receptors (EGF-Rs), c-Met, insulin-like growth factor-1 receptor (IGF-1R), fibroblast growth factor-receptors (FGF-Rs), and non-RTK c-Src can induce EMT and consequently are considered to promote cancer progression.<sup>[4-8]</sup>

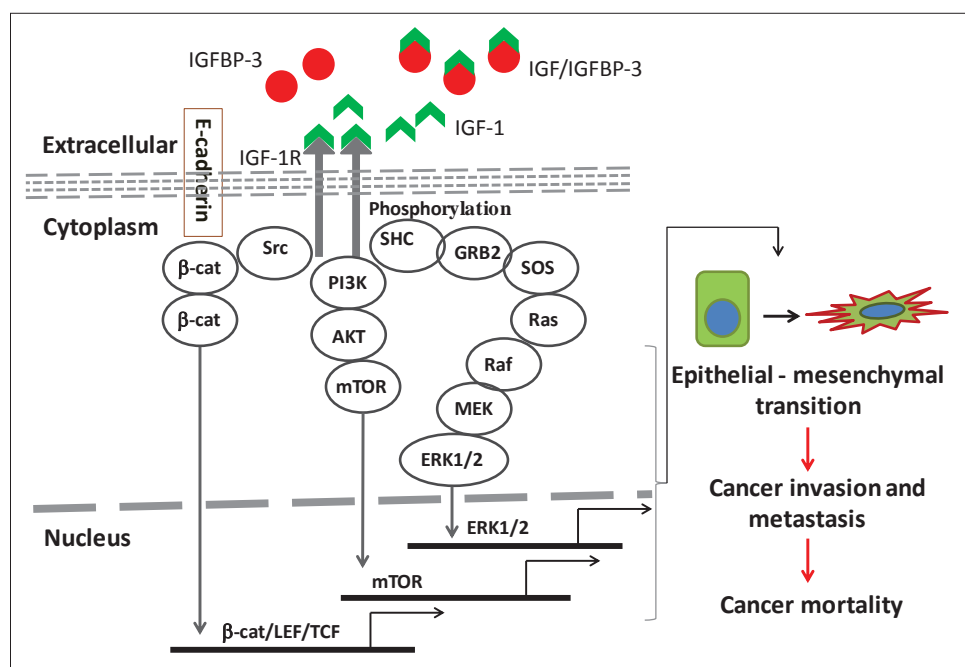
While fewer studies argued that the role of IGF-1R signaling is an important driver of the EMT.<sup>[6]</sup> For instance, in numerous human cancer cell lines, constitutively active EGF-1R dramatically increased cellular migration and invasion. These effects are mediated, at least in part, by its ligand, IGF-1. This growth factor is known to influence cell adhesion through the phosphorylation and transcriptional activation of  $\beta$ -catenin, and dissociation of E-cadherin from the cell membrane, both events being associated with EMT initiation [Figure 1]. Also, it was demonstrated that IGF-1R signaling promotes Akt phosphorylation and protection from apoptosis, which is predicted to limit the efficacy of conventional chemotherapies. In addition, it was reported that IGF-1R pathways (PI3k/Akt/mTOR) and RAF/MEK/ERK1/2 are instrumental in EMT and angiogenesis during tumorigenesis [Figure 1].<sup>[6,9-11]</sup> Thus, there is a strong rationale for the development of IGF-1R targeted therapies, as IGF-1R inhibition might be expected to enhance the effect of cytotoxic chemotherapies or other molecular targeted therapies. Meanwhile and based on Duggan *et al.*<sup>[2]</sup> and our recent publication on the association between fasting, IGF-1R signaling and EMT progression,<sup>[11]</sup> IGF-1R-targeting therapy, including

its downstream inhibitors,<sup>[12]</sup> could constitute a viable therapeutic option for the inhibition of cancer metastasis including breast.

In conclusion, we believe that levels of IGF-1 and potentially the IGF-1/IGFBP-3 ratio play important roles in the initiation of breast cancer invasion and metastasis, and therefore cancer mortality, through EMT progression and deregulation of its key genes [Figure 1]. Thus, we agree with Duggan *et al.*<sup>[2]</sup> that their data need to be confirmed by large cohorts of breast cancer patients and survivors in order to determine the significance of the association between the free IGF-1 and consequently IGF-1R activation and cancer mortality. Meanwhile, we think that more cell based studies are necessary in order to elicit the exact role of IGF-1 and IGF-1/IGFBP-3 ratio in the progression of human breast cancer. We believe that these investigations can help prevent and/or treat human metastatic cancer, including breast, which is responsible for the majority of cancer-related deaths.

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**Figure 1:** Schematic overview showing the relationship between IGF-1, IGFBP-3, IGF-1R signaling pathways, EMT and cancer mortality. IGFBP-3 binds to IGF-1, however, free IGF-1 binds and activates IGF-1R. Thus, IGF-1R downstream-signaling pathways, including Src/β-catenin, PI3k/Akt/mTOR and RAF/MEK/ERK1/2, can be turned-on which leads to the initiation of EMT event and consequently increase cell invasion and metastasis abilities and therefore cancer mortality

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