Tamoxifen induces lymphatic vessels disruption and promotes lymphedema.

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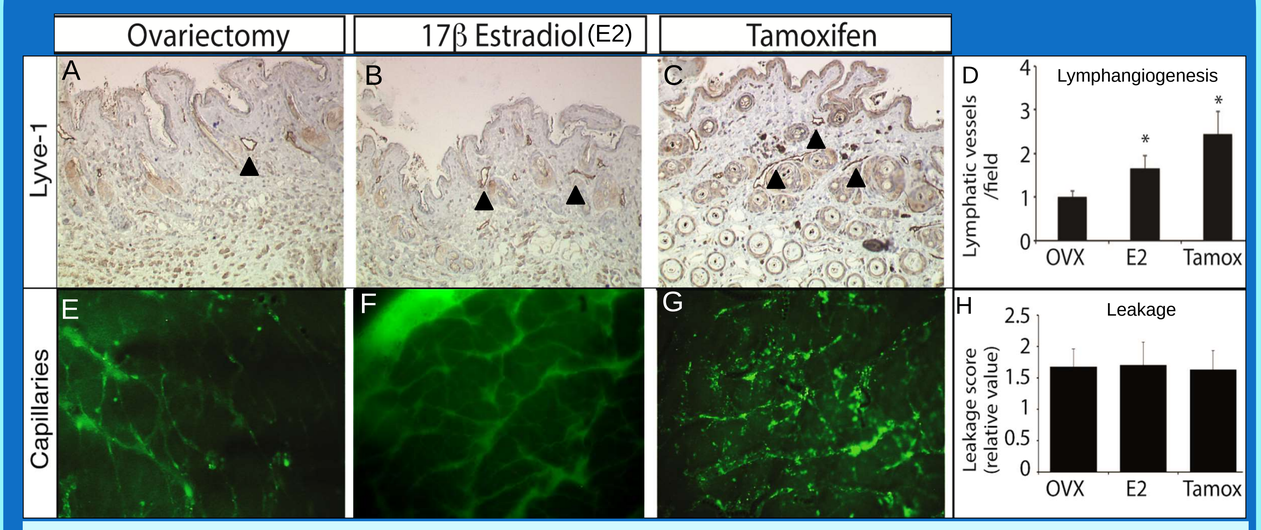
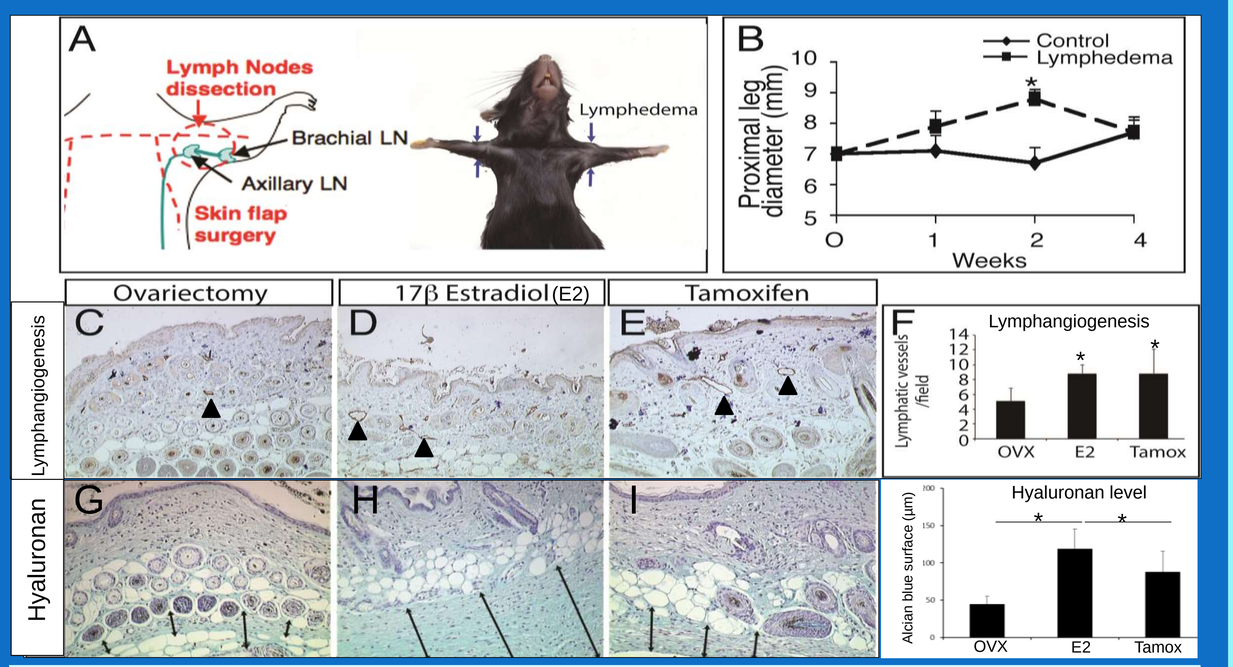
More than 10 percent of breast cancer survivors develop secondary lymphedema within weeks and months after surgery and radiotherapy. Lymphedema refers to a condition of lymphatic dysfunction, which results in a massive fluid and fat accumulation. Although it is a common disabling disease causing significant morbidity, treatment for this chronic pathology remains limited and largely ineffective consisting in massage, restrictive bandaging and dietary restrictions.
This study aim to demonstrate that lymphedema is a complex pathophysiological process rather than a surgical side effect. We evaluated the effect of tamoxifen, the major treatment for breast cancer, in promoting lymphedema. We found that tamoxifen disrupts normal skin drainage and leads to lymphatic leakage. It destabilizes lymphatic network and reduces number of lymphatic endothelial cells filopodia, but has no effect on skin lymphatic density. To mimic the effect of human therapies, we developed a model of mice secondary lymphedema induced by mastectomy associated to axillary lymph nodes dissection. In this model, tamoxifen inhibits lymphatic healing by targeting both lymphatic endothelium and subcutaneous adipose tissue lymphangiogenic growth factor synthesis.
In conclusion, this study demonstrates for the first time the crucial effect of the main drug of breast cancer patients, tamoxifen on lymphatic function. Our work should thus bring new insights for a better understanding on the lymphedema prevalence and constitute a first step to the treatment of secondary lymphedema.

1/ Tamoxifen is an agonist of Estradiol in promoting lymphangiogenesis but disrupts lymphatic drainage



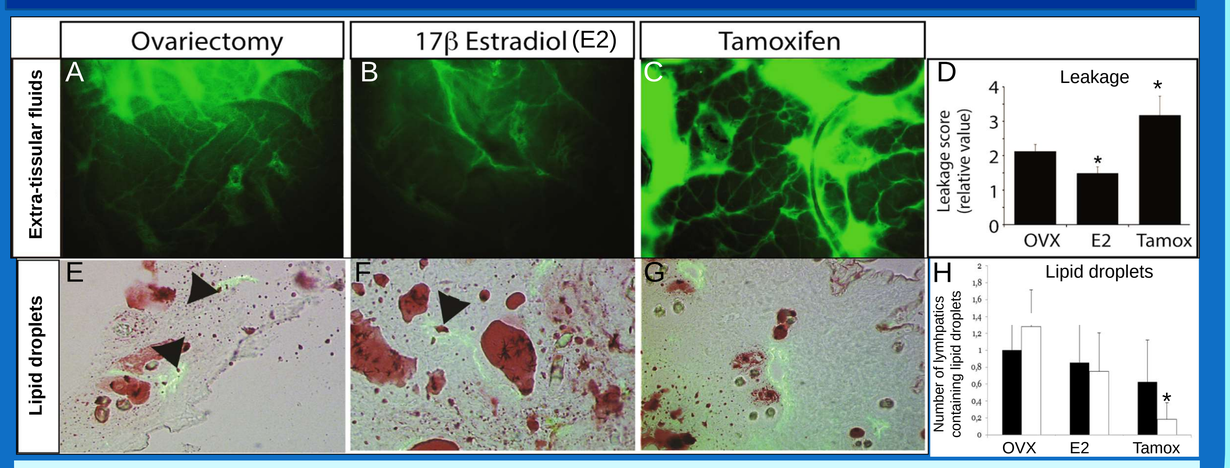
To identify the physiological effects of 17β estradiol and tamoxifen treatments, we performed LYVE-1 immunostaining and lymphangiography in control skins [A-D]. We demonstrated that both treatments promote skin lymphangiogenesis but tamoxifen modify the structure of lymphatic capilaries. Interestingly, despite this disruption, the lymphatic drainage is still functional [E-H].

2/ Tamoxifen and Estradiol promote lymphangiogenesis in lymphedema by inducing hyaluronan synthesis



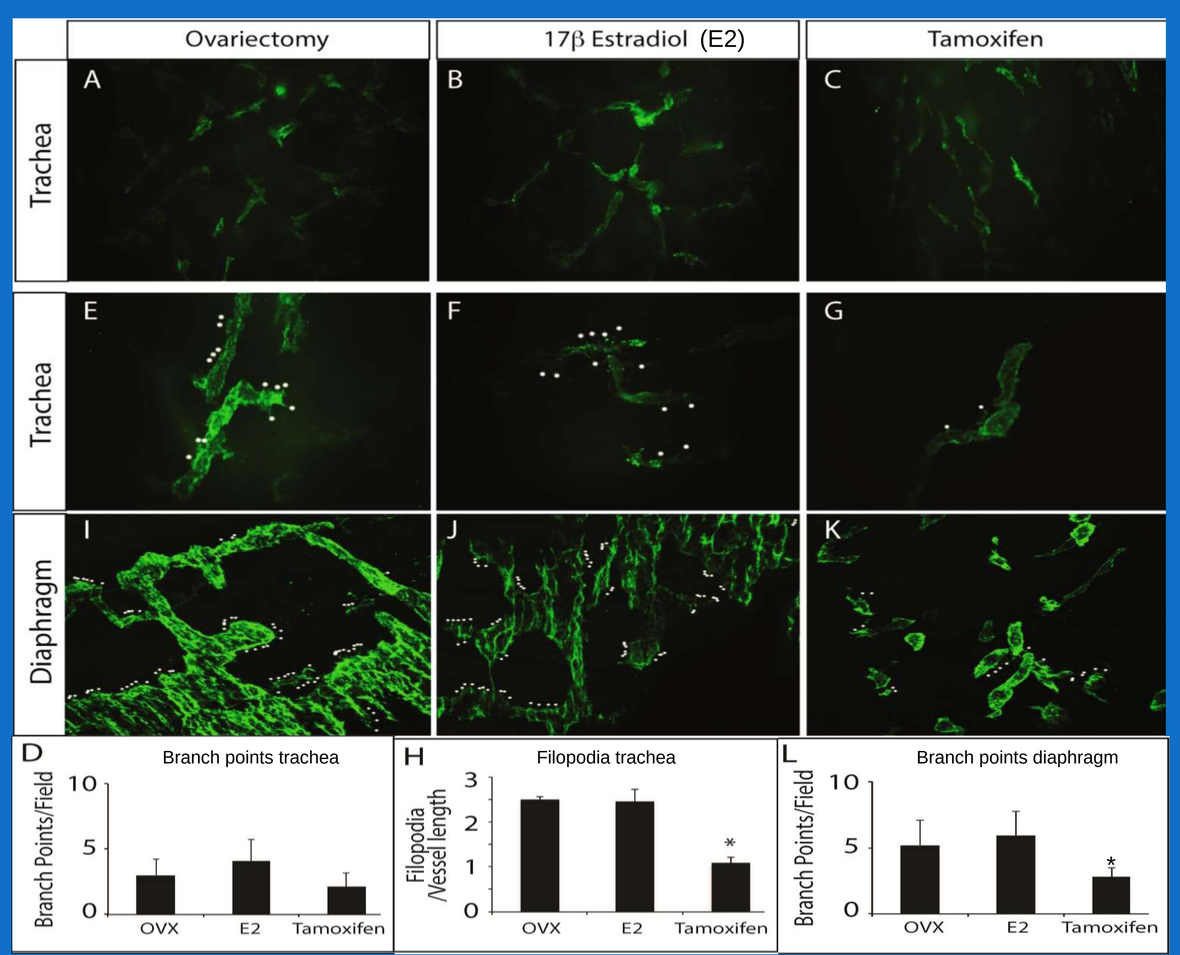
To induce secondary lymphedema, we designed a mice model where we performed a skin flap surgery associated with axillary and brachial lymph nodes dissection [A] . Two weeks after surgery we observed an increase of leg size [B]. As observed in control skins, both treatments promote skin lymphangiogenesis [C-F]. Estradiol and tamoxifen both induce hyaluronic acid synthesis

3/ Tamoxifen impairs lymphatic drainage in lymphedema



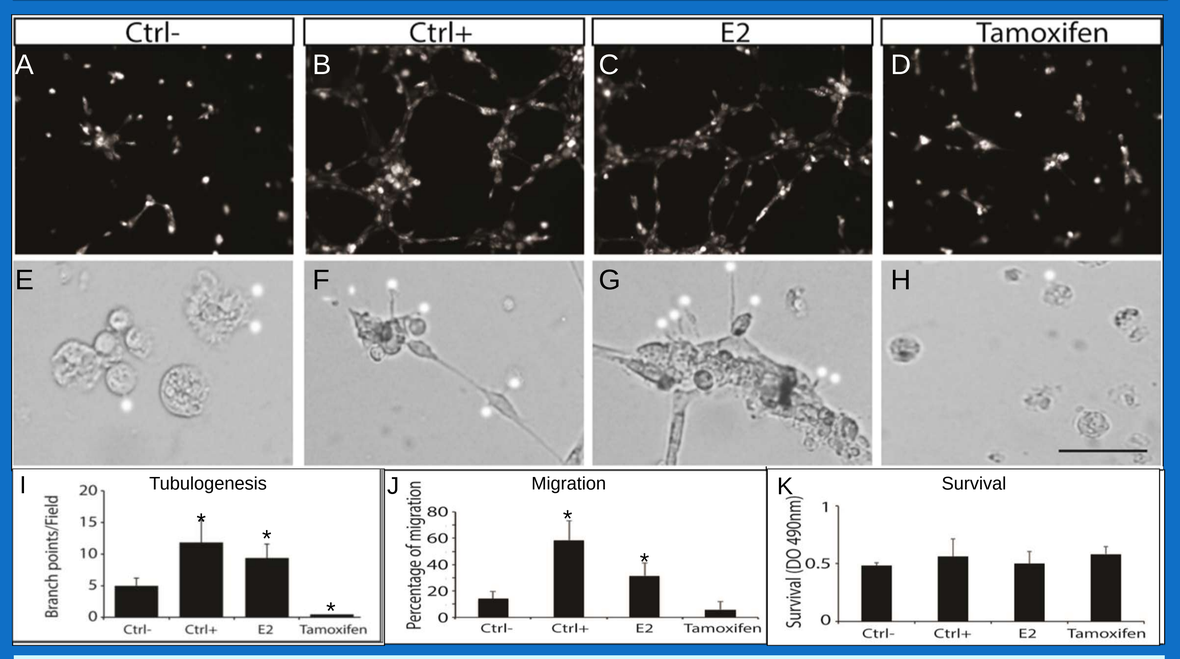
Tamoxifen inhibits drainage of extra-tissular fluids [A-D] and lipids droplets [E-H] by lymphatic vessels.

4/ Tamoxifen disrupts lymphatic network by inhibiting filopodia formation



Whole-mount LYVE-1 staining shows lymphatic disruption in tamoxifen-treated mice trachea [A-G] and diaphragm [I-K], two organs highly vascularised by lymphatics. Tamoxifen inhibits the formation of branch points and filopodia [D-L] and disorganizes the structure of the lymphatic network.

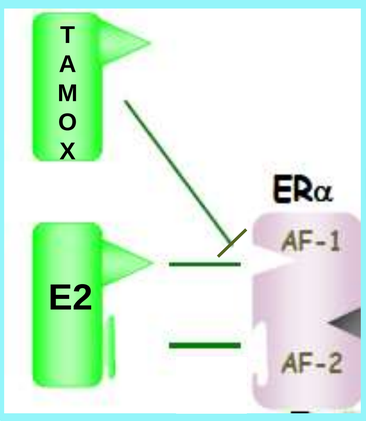
5/ Tamoxifen inhibits estradiol-induced migration and tubulogenesis in HDLEC



In vitro, tamoxifen inhibits Estradiol-induced tubulogenesis [A-D, I], filopodia formation [E-H] and migration [J] but has no effect on survival [K].

Conclusion

Tamoxifen : A risk factor for lymphedema



Lymphatic dysfunction → **Secondary Lymphedema**

→ **A public health challenge**