PS3-03-23 Effects of hormonal contraceptive on tamoxifen efficacy to prevent chemically induced invasive cancers in rats

Oukseub Lee[1], Alexander Eremin[1], Maarten C. Bosland[2], and Seema A. Khan[1]

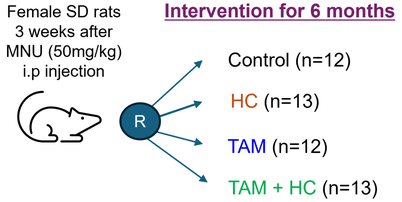
[1] Department of Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL

[2] Department of Pathology, University of Illinois at Chicago, Chicago, IL

BACKGROUND

- Tamoxifen (TAM) is the only anti-estrogen approved for premenopausal women, who are advised to avoid pregnancy but are cautioned against using hormonal contraceptives (HCs).
- This reluctance is based on concerns that HCs used concomitantly with TAM may reduce its efficacy and increase adverse effects.
- These concerns lack direct supporting evidence of harm from HC use in TAM-treated women.
- **We hypothesized that the most widely used combined oral contraceptive (17α-ethinylestradiol and levonorgestrel) would not diminish the tumor-preventive efficacy of oral TAM in a hormonally sensitive, estrogen receptor (ER)-positive mammary tumorigenesis rat model.**

METHODS



Primary Endpoint:
Histopathologically confirmed invasive cancer incidence

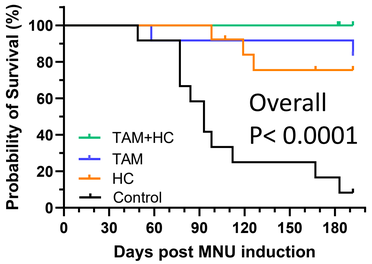
Secondary Endpoints:
- Mammary tumor burden
- Uterine/ovarian safety
- Hormone analysis

Fig. 1. Study schema.

- Female Sprague Dawley (SD) rats at age of 4–5 weeks old received N-Methyl-N-nitrosourea (MNU) at a dose of 50 mg/kg i.p. to induce mammary tumorigenesis. Three weeks later, they were randomized (n=12–13 per group) to control, HC alone, TAM alone, or TAM+HC.
- HC pellets (17α-ethinylestradiol 0.06 mg + levonorgestrel 0.28 mg, 90-day release; Innovative Research of America) were implanted subcutaneously in the dorsal area and replaced at 90 days. TAM was incorporated into the diet (1.03 mg/kg/day in rats, equivalent to daily 7 mg in humans; Inotiv Inc.).
- Rats were monitored for 6 months for mammary tumor formation. Tumor incidence, latency, weights, and volumes were measured. Wet uterine weight was recorded, adjusted for body weight, and processed for histology.

RESULTS

(A) Invasive cancer- free survival



(B) Histopathology of mammary glands and tumors [Ref. 1]

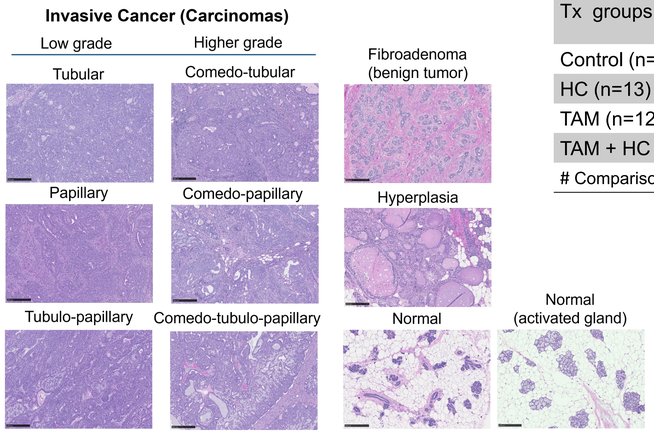


Fig. 2. Cancer prevention study for 6 months. (A) Invasive cancer- free survival. Statistical significance was analyzed with the log-rank test. (B) Representative HE images of histopathological lesions of mammary glands and tumors.

Table 1. Summary of mammary tumor development (number of tumor-bearing rats)

Tx groups	Palpable tumors	Benign tumors	Invasive Cancer	P value#
Control (n=12)	11 (92%)	0 (0%)	11 (92%)	
HC (n=13)	6 (46%)	3 (23%)	3 (23%)	0.0002
TAM (n=12)	2 (17%)	0 (0%)	2 (17%)	0.0001
TAM + HC (n=13)	2 (15%)	2 (15%)	0 (0%)	<0.0001

Comparison to the control group was performed using the log-rank test.

Table 2. Histopathological lesions of mammary glands and tumors

	Number of Carcinomas			
Tx groups	High grade	Low grade	Fibroadenoma	Hyperplasia
Control	5	11	1	0
HC	1	3	3	0
TAM	0	2	2	0
TAM + HC	0	0	3	2

CONCLUSION

- Combined HC (17α-ethinylestradiol + levonorgestrel) did not diminish the cancer-preventive efficacy of oral TAM in this hormonally sensitive, ER-positive mammary tumorigenesis rat model.
- Ongoing histopathology and endocrine biomarker analyses (estrogen, progesterone, follicle stimulating hormone, luteinizing hormone) will assess uterine/ovarian safety and anovulatory status.
- Clinical Implications: If confirmed clinically, allowance of HC use with TAM could increase uptake and adherence of tamoxifen in both high-risk premenopausal women and premenopausal survivors, to whom similar concerns apply.

(A) Mammary cancer burden

(B) Uterine Weight

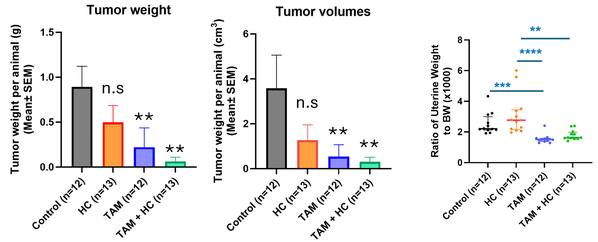


Fig. 3. Evaluation of TAM-response. (A) Tumor burden, assessed by tumor weight and volume, was significantly reduced in the TAM and TAM+HC treatment groups (B) Uterine weights were significantly decreased in the TAM and TAM + HC treatment groups. Statistical significance was assessed using the Kruskal–Wallis test followed by Dunn's post hoc comparisons. p<0.05 (*), p<0.01(**), p<0.001(***), p<0.0001(****).

REFERENCE:

1. Russo et al., Atlas and histologic classification of tumors of the rat mammary gland, J Mammary Gland Biol Neoplasia,. 2000 (PMID: 11149572)

Grant support: the Lynn Sage Breast Cancer Research Foundation (S.A. Khan).

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