# TAMOXIFEN USE INCREASES ENDOMETRIAL CANCER RISK IN PREMENOPAUSAL BREAST CANCER PATIENTS.

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## BACKGROUND and AIMS

- Tamoxifen is indicated in premenopausal patients with HR-positive breast cancer with low to intermediate risk of recurrence as adjuvant endocrine treatment to decrease risk of recurrence and breast cancer mortality, (1,2)
- Previous studies have shown that tamoxifen does not significantly increase the risk of uterine disease in premenopausal women (1,3 4)
- In 2022, Ryu et al published a nationwide cohort study (South Korea) showing a significant increased risk of endometrial cancer related to tamoxifen use in premenopausal women with breast cancer (HR 3,77), after adjusting for confounding factors. (5)
- In Belgium, +- 11,000 patients are diagnosed with BC yearly and +-80% will be HR-positive. A significant number of premenopausal patients will be exposed to tamoxifen. (6)

**Primary endpoint:** Study the relative risk of endometrial cancer in the Belgian population of premenopausal women with breast cancer treated with tamoxifen

## PATIENTS and METHODS

Retrospective, population-based, cohort study

- Data obtained from Belgian Cancer Registry and IMA
- All Belgian women with non-metastasized breast cancer diagnosed between 2008 and 2020
- Divided in 2 groups based on tamoxifen prescriptions
- Occurrence of endometrial cancer any time after breast cancer diagnosis. In tamoxifen group, EC after first prescription.
- Age at time of BC diagnosis: 18 until 53 years
- Approved by ethical committee of UZ Leuven

### Statistics

- Categorical variables: Fishers Exact test
- Continuous variables: Mann-Whitney U-test.
- Primary endpoint: time to development of EC. Cox regression model for analysis of primary endpoint. Multivariate model for confounding factors
- Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

## RESULTS

38857 patients were included in this trial. 23289 (60%) in the tamoxifen group and 15568 (40%) in the control group. Median age was 47 in both groups

Table 1: patient characteristics

| Variable | Statistic | Tamoxifen (n = 23289) | Control (n = 15568) | P-value |
|---|---|---|---|---|
| **Age** | Median | 47 y (18; 53) | 47 y (20; 53) | 0.3586 |
| **Cardiovasc Risk** | n/N (%) | 2537 (10,9%) | 2001 (12,9%) | <0,0001 |
| **Diabetes** | n/N (%) | 531 (2,3%) | 492 (3,2%) | <0,0001 |

Figure 1: Number of patients per incidence year in every group

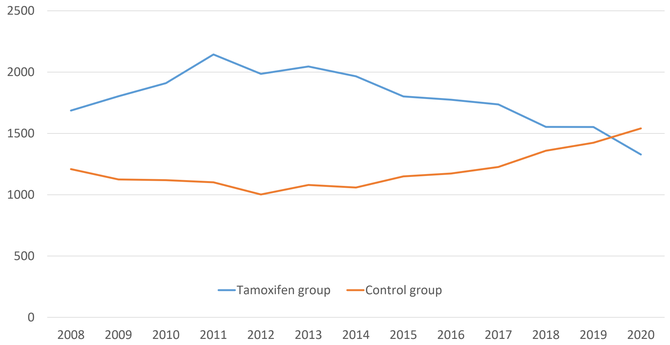



Table 2: Treatment characteristics

| Variable | Statistic | Tamoxifen group | Control group | P-value |
|---|---|---|---|---|
| **(Neo-) adjuvant chemotherapy** | n/N (%) | 10219 (44,6%) | 11105 (75,2%) | <0,0001 |
| **Targeted Therapy*** | n/N (%) | 2676 (11,7%) | 2934 (18,8%) | <0,0001 |
| **Trastuzumab** | n/N (%) | 2600 (11,2%) | 2706 (17,4%) | <0,0001 |
| **Triptoreline/Gosereline** | n/N (%) | 838 (3,6%) | 686 (4,4%) | <0,0001 |

Table 3: Univariate analysis (Cox-model)

| Parameter | Parameter estimate | Standard Error | Chi-square | Pr > ChiSq | HR | 95% HR confidence limits |
|---|---|---|---|---|---|---|
| **Tamoxifen group** | 0,71971 | 0,21793 | 10,9065 | 0,0010 | 2,054 | 1,340 – 3,1481 |

Table 4: Tumour characteristics

| Variable | Statistic | Tamoxifen group | Control group | P-value |
|---|---|---|---|---|
| **Morphology** | n/N (%) | | | P < 0,0001 |
| IDC | | 18803 (80,8%) | 13398 (86,1%) | |
| ILC | | 2878 (12,4%) | 1028 (6,6%) | |
| DCIS | | 188 (0,8%) | 156 (1,0%) | |
| Other | | 1415 (6,1%) | 968 (6,2%) | |
| **pN** | n/N (%) | | | P < 0,0001 |
| pN0 | | 15175 (71,0%) | 8162 (63,2%) | |
| pN1 | | 4896 (22,9%) | 3260 (25,2%) | |
| pN2 | | 967 (4,5%) | 1033 (8,0%) | |
| pN3 | | 338 (1,6%) | 470 (3,6%) | |
| **pT** | n/N (%) | | | P < 0,0001 |
| pT0 | | 359 (1,7%) | 1253 (10,7%) | |
| pT1 | | 14086 (67,9%) | 5698 (48,8%) | |
| pT2 | | 5333 (25,7%) | 3825 (32,7%) | |
| pT3 | | 910 (4,4%) | 822 (7,0%) | |
| pT4 | | 52 (0,3%) | 88 (0,8%) | |
| **Stage** | n/N (%) | | | P < 0,0001 |
| 0 (in situ) | | 1422 (6,1%) | 2026 (13,0%) | |
| I | | 11689 (50,2%) | 3682 (23,4%) | |
| II | | 7710 (33,1%) | 6595 (42,4%) | |
| III | | 2000 (8,6%) | 2533 (16,3%) | |

* Targeted therapy: CDK4/6i, trastuzumab, pertuzumab, trastuzumab-emtansine, bevacizumab, everolimus

Table 5: Multivariate analysis (Cox-model)

| Parameter | Parameter estimate | Standard Error | Chi-square | Pr > ChiSq | HR | 95% HR confidence limits |
|---|---|---|---|---|---|---|
| **Tamoxifen group** | 0.66131 | 0.26933 | 6.0287 | 0.0141 | 1.937 | 1,143-3,284 |
| **Diabetes** | 0.66258 | 0.47161 | 1.9739 | 0.1600 | 1.940 | 0,770-4,889 |
| **Cardiovasc risk** | 0.45409 | 0.26114 | 3.0237 | 0.0821 | 1.575 | 0,944-2,627 |
| **Grade** | -0.13513 | 0.15736 | 0.7375 | 0.3905 | 0.874 | 0,642-1,189 |
| **pN** | -0.17339 | 0.18262 | 0.9015 | 0.3424 | 0.841 | 0,588-1,203 |
| **pT** | 0.01450 | 0.18045 | 0.0065 | 0.9360 | 1.015 | 0,712-1,445 |
| **Chemotherapy** | -0.16585 | 0.26825 | 0.3823 | 0.5364 | 0.847 | 0,501-1,433 |
| **Trastuzumab** | 0.36924 | 0.30409 | 1.4744 | 0.2247 | 1.447 | 0,797-2,625 |
| **GnRH agonist** | 0.11984 | 0.51073 | 0.0551 | 0.8145 | 1.127 | 0,414-3,067 |

## CONCLUSIONS

- This study shows a significantly increased risk of endometrial cancer in premenopausal women with BC treated with tamoxifen, even after adjusting for confounding factors (HR 1,94)
- These findings are not in line with findings from the EBCTG-meta-analysis or ATLAS-trial, and are not included in current guidelines
- Limitations: retrospective study, incomplete data on confounding factors such as definitive menopausal status, risk factors like BMI, WHR, parity, hypertension, hysterectomy.
- Further, qualitative research is warranted

## ABBREVIATIONS

- HR: hormone receptor
- BC: breast cancer
- IMA: Inter Mutualistisch Agentschap (Inter Health Agency)
- EC: endometrial cancer
- DCIS: Ductal Carcinoma In Situ
- WHR: waist-to-hip ratio

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