**Supplementary Tables**

**Table A1**: Primers and restriction enzymes used in PCR-RFLP reactions to investigate selected polymorphisms.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Polymorphism** | **Primer** | **Amplicon (bp)** | **Restriction enzyme** | **RFLP stripe pattern (bp)** | **Reference** |
| *CYP2D6*\*4(rs3892097) | F: 5’-GCCTTCGCCAACCACTCCG-3’ R: 5’-AAATCCTGCTCTTCCGAGGC-3’ | *355* | *MvaI* | \*1/\*1 : 250;105\*1/\*4: 355; 250; 105\*4/\*4:355 | Schur *et al.,* 2001 (84) |
| *CYP3A4*\*1B(rs2740574) | F: 5’-GGAATGAGGACAGCCATAGAGACAAGGGGA-3’R: 5’-CCTTTCAGCTCTGTGTTGCTCTTTGCTG-3’ | *385* | *MboII* | \*1/\*1: 175;169\*1/\*1B:210;175;169\*1B/\*1B:210;175 | Cavalli *et al.,* 2001 (85) |
| *CYP3A5*\*3(rs776746) | F: 5’-CTTTAAAGAGCTCTTTTGTCTCTCA-3’R: 5’-GAAGCCAGACTTTGATCATTATGTTATG-3’ | *196* | *BseMII* | \*1/\*1: 196\*1/\*3:196;160;36\*3/\*3:160;36 | Lee *et al.,* 2005 (15) |
| *SULT1A1*\*2(rs928286) | F: 5'-GTTGGCTCTGCAGGGTTTCTAGGA-3' R: 5'-CCCAAACCCCCTGCTGGCCAGCACCC-3' | *333* | *HaeII* | \*1/\*1:168;165\*1/\*2:333;168;165\*2/\*2:333 | Arslan *et al.,* 2011 (55) |
| *UGT2B7*\*2(rs743936) | F: 5’-TTGCCTACATTTTTGCCTACA-3’ R: 5’-CGTGCACATGAGTTTCTAATTG-3’.  | *400* | *BseGI* | \*1/\*1:332;68\*1/\*2:332;221;111;68\*2/\*2:221;111;68 | Kagaya *et al.,* 2007 (86) |
| *UGT2B15*\*2(rs1902023) | F: 5’-CTGTGGAAAGGTGCTAGT-3’ R: 5’-GAATTTTCAGAAGAGAATCTTCCAGAT-3’  | *215* | *Sau3AI* | \*1/\*1: 215\*1/\*2:215;187\*2/\*2:187 | Hajdinjak *et al.,* 2004 (87) |
| *ESR1*V364E(rs121913044) | F: 5’-ACAAGCGCCAGAGAGATGAT-3’ R: 5’-CCCCACTATTTCTCCCATGA-3’  | *376* | *BanI* | 364V/364V:290;86364V/364E:376;290;86364E/364E:376 |  |

**Table A2**.- Steady-state plasma concentration of TAM, N-desmethylTAM, 4-hydroxyTAM and endoxifen, and concentration of 17β estradiol, according to *CYP2D6\*4* (rs3892097), *CYP3A4\*1B* (rs2740574), *CYP3A5\*3* (rs776746), *SULT1A1\*2* (rs9282861), *UGT2B7\*2* (rs7439366), *UGT2B15\*2* (rs1902023) and *ESR1 V364E* (rs121913044) genetic polymorphisms.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***Total N*** | ***CYP2D6 \*1/\*1*** | ***CYP2D6 \*1/\*4*** | **CYP2D6 \*4/\*4** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [NdesMeTAM]/[TAM] | 37 | 30 | 59 ± 15 | 7 | 55 ± 12 | 0 |  | 0.672# | 0.603\*\*\*\* | 0.598 |
| [4OHTAM]/[TAM] | 37 | 30 | 0.09 ± 0.05 | 7 | 0.06 ± 0.03 | 0 |  | 0.235# | 0.249\*\*\*\* | 0.248 |
| [endoxifen]/[NdesMeTAM] | 40 | 33 | 0.01 ± 0.01 | 7 | 0.005 ± 0.001 | 0 |  | <0.0001# | 0.827\*\*\* | 0.685 |
| [endoxifen]/[4OHTAM] | 40 | 33 | 3 ± 1 | 7 | 4 ± 1 | 0 |  | 0.538# | 0.080\*\*\*\* | 0.080 |
| [17βestradiol], pg/mL | 25 | 20 | 108 ± 197 | 5 | 64 ± 70 | 0 |  | 0.058# | 0.603\*\*\*\* | 0.633 |
|  |  | ***CYP3A4 \*1/\*1*** | ***CYP3A4 \*1/\*1B*** | **CYP3A4 \*1B/\*1B** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [NdeMeTAM]/[TAM] | 37 | 33 | 58 ± 15 | 4 | 60 ± 10 | 0 |  | 0.520# | 0.742\*\*\*\* | 0.768 |
| [4OHTAM]/[TAM] | 37 | 33 | 0.08 ± 0.04 | 4 | 0.11 ± 0.03 | 0 |  | 0.811# | 0.327\*\*\*\* | 0.328 |
| [endoxifen]/[4OHTAM] | 40 | 35 | 4 ± 1 | 5 | 2.0 ± 1.0 | 0 |  | 0.445# | **0.041\*\*\*\*** | **0.041** |
| [17βestradiol], pg/mL | 25 | 23 | 70 ± 99 | 2 | 434 ± 556 | 0 |  | -- | 0.140\*\*\* | **0.003** |
|  |  | ***CYP3A5 \*1/\*1*** | ***CYP3A5 \*1/\*3*** | **CYP3A5 \*1/\*3** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [NdeMeTAM]/[TAM] | 37 | 0 | 0 | 17 | 61 ± 13 | 20 | 56 ± 16 | 0.579# | 0,299\*\*\*\* | 0.289 |
| [4OHTAM]/[TAM] | 37 | 0 | 0 | 17 | 0.08 ± 0.03 | 20 | 0.08 ± 0.05 | 0.035# | 0.757\*\*\* | 0.328 |
| [endoxifen]/[4OHTAM] | 40 | 0 | 0 | 18 | 4 ± 1 | 22 | 3 ± 1 | 0.518# | 0.459\*\*\*\* | 0.614 |
| [17βestradiol], pg/mL | 25 | 0 | 0 | 9 | 115 ± 267 | 16 | 90 ± 113 | 0.004# | 0.856\*\*\* | 0.745 |
|  |  | ***SULT1A1 \*1/\*1*** | ***SULT1A1 \*1/\*2*** | **SULT1A1 \*2/\*2** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [4OHTAM], ng/mL | 40 | 8 | 4 ± 3 | 20 | 6 ± 2 | 12 | 5 ± 3 | 0.597$ | 0,557\*\* | 0.706 |
| [Endoxifen], ng/mL | 40 | 8 | 19 ± 7 | 20 | 21 ± 11 | 12 | 21 ± 12 | 0.772$ | 0,851\*\* | 0.700 |
| [17βEstradiol], pg/mL | 25 | 4 | 15 ± 2 | 14 | 146 ± 225 | 7 | 52 ± 76 | 0.088$ | 0.321\*\* | 0.988 |
|  |  | ***UGT2B7 \*1/\*1*** | ***UGT2B7 \*1/\*2*** | **UGT2B7 \*2/\*2** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [4OHTAM], ng/mL | 40 | 4 | 4 ± 2 | 18 | 6 ± 2 | 18 | 5 ± 3 | 0.436$ | 0.543\*\* | 0.903 |
| [17βEstradiol], pg/mL | 25 | 1 | 174 ± 0 | 11 | 163 ± 251 | 13 | 39 ± 56 | -- | 0.340\* | 0.097 |
|  |  | ***UGT2B15 \*1/\*1*** | ***UGT2B15 \*1/\*2*** | **UGT2B15 \*2/\*2** |  |  |  |
|  |  | n | *Mean* ± SD | n | *Mean* ± SD | n | *Mean* ± SD | *p-value* | *p-value* | *p-value* |
| [4OHTAM], ng/mL |  | 4 | 5 ± 3 | 33 | 5 ± 3 | 3 | 5 ± 2 | 0.985$ | 0.982\*\* | 0.924 |
| [17βEstradiol], pg/mL |  | 3 | 16 ± 1 | 20 | 119 ± 196 | 2 | 23 ± 0 | -- | 0.603\* | 0.816 |

*TAM: Tamoxifen. NdesMeTAM: N-desmethylTAM. 4OHTAM: 4-hydroxyTAM. Mean: Average. SD: Standard deviation.*  # *F-test in Unpaired t test with Welch's correction:p>0.05 the group were parametric,, p<0.05 the group were non-parametric; $* Welch's ANOVA test in Brown-Forsythe and Welch ANOVA tests, *p>0.05 the group were parametric,, p<0.05 the group were non-parametric*; *\*\*\*\*Unpaired t test for* *parametric data; \*\*\** *Mann-Whitney test for non-parametric data; \*\***Ordinary one-way ANOVA for parametric data; \** *Kruskal-Wallis test for non-parametric data.& Linear regression for bivariable analysis*

**Table A3:** Demographic aspects of patients with [NdesMeTAM]/[TAM], [4OHTAM]/[TAM], [Endoxifen]/[NdesMeTAM], [Endoxifen]/[4OHTAM, AND 17βEstradiol greater than or equal to the average (cases) and less than average (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | [NdesMeTAM]/[TAM] | [4OHTAM]/[TAM] | [Endoxifen]/[NdesMeTAM] |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
|  | n | *Mean±SD* | n | *Mean±SD* | n | *Mean±SD* | n | *Mean±SD* | n | *Mean±SD* | n | *Mean±SD* |
| **Anthropometric Characteristics** |
| Age (years) | 18 | 59±10 | 21 | 58±11 | 0.7 | 36 | 58±10 | 3 | 56±12 | 0.6 | 29 | 59±10 | 10 | 57±11 | 0.5 |
| Weight, (Kg) | 19 | 65±14 | 21 | 74±16 | 0.5 | 37 | 68±15 | 3 | 86±23 | **0.1** | 30 | 71±15 | 10 | 65±18 | **0.2** |
| Height, (m) | 18 | 1.54±0.06 | 21 | 1.55±0.05 | 0.6 | 36 | 1.54±0.05 | 3 | 1.54±0.04 | 0.9 | 29 | 1.55±0.06 | 10 | 1.53±0.04 | **0.2** |
| BMI (Kg/m2) | 18 | 27±5 | 21 | 30±6 | **0.06** | 36 | 28±5 | 3 | 34±7 | **0.1** | 29 | 29±6 | 10 | 27±6 | 0.3 |
| **Socio-genetic gradient** |
| Blood type |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| AB | 0 |  | 1 |  | 0.3 | 1 |  | 0 |  | - | 1 |  | 0 |  | 0.5 |
| A | 5 |  | 4 |  | 9 |  | 0 |  | 8 |  | 1 |  |
| B | 1 |  | 0 |  | 1 |  | 0 |  | 0 |  | 1 |  |
| O | 7 |  | 13 |  | 17 |  | 3 |  | 15 |  | 5 |  |
| Number of members in the family | 19 | 3±1 | 21 | 3±1 | 0.5 | 37 | 3±1 | 16 | 4±2 | 0.4 | 30 | 3±1 | 10 | 3±2 | 0.6 |
| **Socioeconomic** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <$CLP135,000 (U$ 200) | 3 |  | 5 |  | 0.4 | 7 |  | 1 |  | 0.9 | 5 |  | 3 |  | 0.6 |
| $CLP135,001-500,000 (U$ 200-750) | 10 |  | 13 |  | 22 |  | 1 |  | 18 |  | 5 |  |
| $CLP 500,001-1,000,000 (U$ >750-1,450) | 6 |  | 3 |  | 8 |  | 1 |  | 7 |  | 2 |  |
| **Risk factor's** |
| Alcoholic Habit Presence | - |  | - |  | - | - |  | - |  | - | - |  | - |  | - |
| Smoking Habit | 3 |  | 7 |  | **0.1** | 8 |  | 2 |  | 0.1 | 6 |  | 4 |  | **0.2** |
| Family history of cancer (any besides BC or OC) | 13 |  | 11 |  | **0.2** | 21 |  | 3 |  | - | 17 |  | 7 |  | 0.4 |
| Family History of breast (BC) or ovary cancer (OC) | 8 |  | 7 |  | 0.5 | 13 |  | 2 |  | **0.2** | 10 |  | 5 |  | 0.3 |

*[NdesMeTAM]/[TAM]’s mean was 58.65; [4OHTAM]/[TAM]’s mean was 0.087; [Endoxifen]/[NdesMeTAM]’s mean was 0.0075; [Endoxifen]/[4OHTAM]’s mean was 3.99; 17βEstradiol’s mean was 99.36 \*Logistic regression.*

Continue Table SIII

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | [Endoxifen]/[4OHTAM] |  |  | 17βEstradiol |  |  |  |
|  |  | *Control* |  | *Cases* | *p-value* |  | *Control* |  | *Cases* | *p-value* |
|  | n | *Mean±SD* | n | *Mean±SD* |  | n | *Mean±SD* | n | *Mean±SD* |  |
| **Anthropometric Characteristics** |  |  |  |  |  |  |  |  |  |  |
| Age (years) | 20 | 58±10 | 19 | 59±11 | 0.7 | 18 | 58±9 | 6 | 57±13 | 0.8 |
| Weight, (Kg) | 20 | 71±16 | 20 | 68±15 | 0.5 | 19 | 66±12 | 6 | 70±16 | 0.5 |
| Height, (m) | 19 | 1.54±0.05 | 20 | 1.54±0.05 | 0.8 | 18 | 1.55±0.05 | 6 | 1.56±0.05 | 0.7 |
| BMI (Kg/m2) | 19 | 29±6 | 20 | 28±6 | 0.5 | 18 | 27±5 | 6 | 28±5 | 0.6 |
| **Socio-genetic gradient** |  |  |  |  |  |  |  |  |  |  |
| Blood type |  |  |  |  |  |  |  |  |  |  |
| AB | 1 |  | 0 |  | 0.5 | 0 |  | 0 |  | 0.8 |
| A | 5 |  | 4 |  |  | 4 |  | 1 |  |  |
| B | 1 |  | 0 |  |  | 1 |  | 0 |  |  |
| O | 11 |  | 9 |  |  | 9 |  | 3 |  |  |
| Number of members in the family | 20 | 3±1 | 20 | 3±1 | 0.7 | 19 | 3±1 | 6 | 3±1 | 0.8 |
| **Socioeconomic** |  |  |  |  |  |  |  |  |  |  |
| <$CLP135,000 (U$ 200) | 5 |  | 3 |  | 0.4 | 5 |  | 1 |  | 0.7 |
| $CLP135,001-500,000 (U$ 200-750) | 12 |  | 11 |  |  | 10 |  | 3 |  |  |
| $CLP 500,001-1,000,000 (U$ >750-1,450) | 3 |  | 6 |  |  | 4 |  | 2 |  |  |
| **Risk factor's** |  |  |  |  |  |  |  |  |  |  |
| Alcoholic Habit Presence | - |  | - |  | - | - |  | - |  | - |
| Smoking Habit | 5 |  | 5 |  | 1.0 | 4 |  | 2 |  | 0.5 |
| Family history of cancer (any besides BC or OC) | 14 |  | 10 |  | **0.1** | 13 |  | 4 |  | 0.9 |
| Family History of breast (BC) or ovary cancer (OC) | 8 |  | 7 |  | 0.7 | 8 |  | 4 |  | **0.2** |

**Table A4:** Gynecological and Pathological features of patients with [NdesMeTAM]/[TAM], [4OHTAM]/[TAM], [Endoxifen]/[NdesMeTAM], [Endoxifen]/[4OHTAM, AND 17βEstradiol greater than or equal to the average (cases) and less than average (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **[NdesMeTAM]/[TAM]** | **[4OHTAM]/[TAM]** | **[Endoxifen]/[NdesMeTAM]** |
|  | ***Control*** | ***Cases*** | ***p-value*** | ***Control*** | ***Cases*** | ***p-value*** | ***Control*** | ***Cases*** | ***p-value*** |
|  | **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** |
| **Gynecological Characteristics** |
| Menarche age (years) | 19 | 11±1 | 21 | 13±2 | **0.02** | 37 | 12±2 | 3 | 13.6±0.5 | 0.4 | 30 | 12±1 | 10 | 13±2 | **0.1** |
| Number of Gestations | 19 | 3±2 | 21 | 2±1 | 0.4 | 37 | 2±2 | 3 | 3±2 | 0.9 | 30 | 3±2 | 10 | 2±1 | 0.4 |
| Number of deliveries | 19 | 2±2 | 21 | 2±1 | 0.8 | 37 | 2±1 | 3 | 2±1 | 0.8 | 30 | 2±1 | 10 | 1±1 | **0.1** |
| Number of Abortions | 19 | 1±1 | 21 | 0.3±0.4 | **0.08** | 37 | 0.5±0.8 | 3 | 0.3±0.5 | 0.6 | 30 | 0.4±0.6 | 10 | 1±1 | 0.3 |
| Breastfeeding time (months) | 16 | 24±31 | 19 | 27±25 | 0.7 | 33 | 26±28 | 2 | 28±27 | 0.9 | 26 | 28±30 | 9 | 19±9 | 0.3 |
| Oral Contraceptive Treatment (months) | 19 | 51±89 | 21 | 50±79 | 0.9 | 37 | 55±83 | 3 | 1±1 | **0.08** | 30 | 66±89 | 10 | 4±11 | **0.006** |
| **Menopausal status** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Premenopausal | 5 |  | 9 |  | **0.2** | 12 |  | 2 |  | **0.2** | 11 |  | 3 |  | 0.6 |
| Postmenopausal | 14 |  | 12 |  | 25 |  | 1 |  | 19 |  | 7 |  |
| Treatment with HRT for menopause (months) | 19 | 5±15 | 19 | 3±9 | 0.6 | 35 | 3±12 | 3 | 12±20 | 0.3 | 29 | 9±13 | 9 | 4±12 | 0.9 |
| **Pathological Features** |
| Age of diagnosis (years) | 19 | 54±11 | 20 | 54±11 | 0.8 | 36 | 54±11 | 3 | 52±12 | 0.7 | 29 | 54±11 | 10 | 53±11 | 0.6 |
| **Cancer stage at diagnosis** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| I | 8 |  | 7 |  | 0.8 | 14 |  | 1 |  | 0.7 | 9 |  | 6 |  | **0.2** |
| II | 9 |  | 12 |  | 19 |  | 2 |  | 18 |  | 3 |  |
| III | 2 |  | 2 |  | 4 |  | 0 |  | 3 |  | 1 |  |
| **Tumor Histology** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ductal carcinoma in situ | 1 |  | 0 |  | -- | 1 |  | 0 |  | - | 1 |  | 0 |  | --- |
| Invasive Ductal Carcinoma  | 15 |  | 20 |  | 32 |  | 3 |  | 26 |  | 9 |  |
| Invasive Lobular Carcinoma  | 1 |  | 0 |  | 1 |  | 0 |  | 0 |  | 1 |  |
| Others, (IBC, IPC, etc.) | 2 |  | 0 |  | 1 |  | 0 |  | 2 |  | 0 |  |
| **Cell Differentiation Degree** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| G1 | 4 |  | 4 |  | 0.6 | 7 |  | 1 |  | 0.7 | 6 |  | 2 |  | 0.9 |
| G2 | 8 |  | 11 |  | 18 |  | 1 |  | 14 |  | 5 |  |
| G3 | 2 |  | 5 |  | 6 |  | 1 |  | 5 |  | 2 |  |
| Treatment before to TAM |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Surgery | 0 |  | 3 |  | **0.08** | 3 |  | 0 |  | **0.1** | 3 |  | 0 |  | --- |
| Surgery + radiotherapy | 5 |  | 4 |  | 8 |  | 1 |  | 5 |  | 4 |  |
| Surgery + chemotherapy  | 0 |  | 2 |  | 1 |  | 1 |  | 0 |  | 2 |  |
| Surgery + chemotherapy + radiotherapy | 4 |  | 2 |  | 6 |  | 0 |  | 6 |  | 0 |  |

*[NdesMeTAM]/[TAM]’s mean was 58.65; [4OHTAM]/[TAM]’s mean was 0.087; [Endoxifen]/[NdesMeTAM]’s mean was 0.0075; [Endoxifen]/[4OHTAM]’s mean was 3.99; 17βEstradiol’s mean was 99.36 \*Logistic regression.*

Continue Table A4

|  |  |
| --- | --- |
| **[Endoxifen]/[4OHTAM]** | **17βEstradiol** |
| **Control** | **Cases** | **p-value** | **Control** | **Cases** | **p-value** |
| **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** | **n** | **Mean±SD** |
|  |
| 20 | 12±1 | 20 | 12±2 | 0.4 | 19 | 12±1 | 6 | 13±3 | **0.1** |
| 20 | 2±1 | 20 | 3±2 | **0.1** | 19 | 2±2 | 6 | 2±1 | 0.9 |
| 20 | 2±1 | 20 | 2±2 | 0.4 | 19 | 2±1 | 6 | 1±1 | 0.8 |
| 20 | 0.3±0.4 | 20 | 1±1 | **0.1** | 19 | 0.4±0.9 | 6 | 0.6±0.8 | 0.5 |
| 18 | 30±30 | 17 | 22±24 | 0.3 | 17 | 22±28 | 5 | 16±15 | 0.5 |
| 20 | 34±73 | 20 | 67±87 | **0.1** | 19 | 39±82 | 6 | 52±54 | 0.7 |
|  |  |  |  |  |  |  |  |  |  |
| 6 |  | 8 |  | 0.5 | 5 |  | 3 |  | **0.2** |
| 14 |  | 12 |  | 14 |  | 3 |  |
| 19 | 3±11 | 19 | 4±14 | 0.8 | 19 | 6±17 | 4 | 6±12 | 0.9 |
|  |
| 20 | 54±11 | 19 | 53±11 | 0.8 | 18 | 53±9 | 6 | 52±14 | 0.8 |
|  |  |  |  |  |  |  |  |  |  |
| 9 |  | 6 |  | 0.6 | 11 |  | 2 |  | 0.4 |
| 11 |  | 10 |  | 7 |  | 3 |  |
| 0 |  | 4 |  | 1 |  | 1 |  |
|  |  |  |  |  |  |  |  |  |  |
| 0 |  | 1 |  | 0.4 | 1 |  | 0 |  | --- |
| 19 |  | 16 |  | 14 |  | 6 |  |
| 0 |  | 1 |  | 1 |  | 0 |  |
| 1 |  | 1 |  | 2 |  | 0 |  |
|  |  |  |  |  |  |  |  |  |  |
| 5 |  | 3 |  | 0.4 | 3 |  | 1 |  | 0.6 |
| 9 |  | 10 |  | 8 |  | 3 |  |
| 5 |  | 2 |  | 2 |  | 2 |  |
|  |  |  |  |  |  |  |  |  |  |
| 3 |  | 0 |  | 0.3 | 1 |  | 0 |  | 0.4 |
| 6 |  | 3 |  | 6 |  | 2 |  |
| 0 |  | 2 |  | 1 |  | 0 |  |
| 5 |  | 1 |  | 2 |  | 2 |  |

**Table A5:** Genotypic and allelic frequencies of CYP2D6\*4 (rs3892097), CYP3A4\*1B (rs2740574), CYP3A5\*3 (rs776746), SULT1A1\*2 (rs9282861), UGT2B7\*2 (rs7439366), UGT2B15\*2 (rs1902023), and ESR1 V364E (rs121913044) polymorphisms in patients with [NdesMeTAM]/[TAM], [4OHTAM]/[TAM], [Endoxifen]/[NdesMeTAM], [Endoxifen]/[4OHTAM, AND 17βEstradiol greater than or equal to the average (cases) and less than average (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | [NdesMeTAM]/[TAM] | [4OHTAM]/[TAM] | [Endoxifen]/[NdesMeTAM] |
|  | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value |
| **Enzymes involved in the activation of TAM** |
| **CYP2D6** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 14 | 19 | **0.1** | 30 | 3 | -- | 24 | 9 | 0.4 |
| \*1/\*4 (GA) | 5 | 2 | 7 | 0 | 6 | 1 |
| \*4/\*4 (AA) | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A4** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 18 | 17 | **0.1** | 33 | 2 | 0.3 | 27 | 8 | 0.4 |
| \*1/\*1B (AG) | 1 | 4 | 4 | 1 | 3 | 2 |
| \*1B/\*1B (GG) | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A5** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 0 | 0 | 0.3 | 0 | 0 | 0.6 | 0 | 0 | 0.7 |
| \*1/\*3 (AG) | 7 | 11 | 17 | 1 | 14 | 4 |
| \*3/\*3 (GG) | 12 | 10 | 20 | 2 | 16 | 6 |
| Enzymes involved in the elimination of TAM and its metabolites |
| **SULT1A1** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 3 | 5 | 0.6 | 7 | 1 | 0.8 | 6 | 2 | 0.7 |
| \*1/\*2 (GA) | 9 | 11 | 18 | 2 | 16 | 4 |
| \*2/\*2 (AA) | 7 | 5 | 12 | 0 | 8 | 4 |
| \*1/\*1 (GG) | 3 | 5 | 0.5 | 7 | 1 | 0.5 | 6 | 2 | 1.0 |
| \*1/\*2 (GA)+\*2/\*2 (AA) | 16 | 16 | 30 | 2 | 24 | 8 |
| \*1/\*1 (GG)+\*1/\*2 (GA) | 12 | 16 | 0.3 | 25 | 3 | --- | 22 | 6 | 0.4 |
| \*2/\*2 (AA) | 7 | 5 | 12 | 0 | 8 | 4 |
| **UGT2B7** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (TT) | 1 | 3 | **0.2** | 1 | 3 | **0.03** | 2 | 2 | 0.5 |
| \*1/\*2 (TC) | 7 | 11 | 9 | 9 | 14 | 4 |
| \*2/\*2 (CC) | 11 | 7 | 14 | 4 | 14 | 4 |
| \*1/\*1 (TT) | 1 | 3 | 0.3 | 1 | 3 | **0.01** | 2 | 2 | **0.2** |
| \*1/\*2 (TC)+\*2/\*2 (CC) | 18 | 18 | 23 | 13 | 28 | 8 |
| \*1/\*1 (TT)+\*1/\*2 (TC) | 8 | 14 | **0.1** | 10 | 12 | 0.6 | 16 | 6 | 0.7 |
| \*2/\*2 (CC) | 11 | 7 | 14 | 4 | 14 | 4 |
| **UGT2B15** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 2 | 2 | 0.7 | 2 | 2 | **0.2** | 2 | 2 | **0.2** |
| \*1/\*2 (AC) | 15 | 18 | 18 | 0 | 25 | 8 |
| \*2/\*2 (CC) | 2 | 1 | 17 | 1 | 3 | 0 |
| \*1/\*1 (AA) | 2 | 2 | 0.9 | 2 | 2 | **0.2** | 2 | 2 | **0.2** |
| \*1/\*2 (AC)+\*2/\*2 (CC) | 17 | 19 | 35 | 1 | 28 | 8 |
| \*1/\*1 (AA)+\*1/\*2 (AC) | 17 | 20 | 0.4 | 20 | 2 | --- | 27 | 10 | --- |
| \*2/\*2 (CC) | 2 | 1 | 17 | 1 | 3 | 0 |
| **Estrogen receptor. TAM therapeutic target** |
| **ESR1 V364E** |  |  |  |  |  |  |  |  |  |
| 364V/364V (TT) | 13 | 13 | 0.8 | 24 | 2 | 0.6 | 20 | 6 | 0.8 |
| 364V/364E (TA) | 3 | 5 | 7 | 1 | 6 | 2 |
| 364E/364E (AA) | 3 | 3 | 6 | 0 | 4 | 2 |
| 364V/364V (TT) | 13 | 13 | 0.6 | 24 | 2 | 0.9 | 20 | 6 | 0.7 |
| 364V/364E (TA) + 364E/364E (AA)  | 6 | 8 | 13 | 1 | 10 | 4 |
| 364V/364V (TT)+ 364V/364E (TA) | 16 | 18 | 0.8 | 31 | 3 | --- | 26 | 8 | 0.6 |
| 364E/364E (AA) | 3 | 3 | 6 | 0 | 4 | 2 |

*[NdesMeTAM]/[TAM]’s mean was 58.65; [4OHTAM]/[TAM]’s mean was 0.087; [Endoxifen]/[NdesMeTAM]’s mean was 0.0075; [Endoxifen]/[4OHTAM]’s mean was 3.99; 17βEstradiol’s mean was 99.36 \*Logistic regression**.*

Continue Table A5

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | [Endoxifen]/[4OHTAM] |  | 17βEstradiol |  |  |
|  | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value |
| **Enzymes involved in the activation of TAM** |  |  |  |  |  |  |
| **CYP2D6** |  |  |  |  |  |  |
| \*1/\*1 (GG) | 18 | 15 | **0.2** | 15 | 5 | 0.8 |
| \*1/\*4 (GA) | 2 | 5 |  | 4 | 1 |  |
| \*4/\*4 (AA) | 0 | 0 |  | 0 | 0 |  |
| **CYP3A4** |  |  |  |  |  |  |
| \*1/\*1 (AA) | 16 | 19 | **0.1** | 18 | 5 | 0.4 |
| \*1/\*1B (AG) | 4 | 1 |  | 1 | 1 |  |
| \*1B/\*1B (GG) | 0 | 0 |  | 0 | 0 |  |
| **CYP3A5** |  |  |  |  |  |  |
| \*1/\*1 (AA) | 0 | 0 | 0.5 | 0 | 0 | **0.2** |
| \*1/\*3 (AG) | 8 | 10 |  | 8 | 1 |  |
| \*3/\*3 (GG) | 12 | 10 |  | 11 | 5 |  |
| Enzymes involved in the elimination of TAM and its metabolites |  |  |  |  |  |  |
| **SULT1A1** |  |  |  |  |  |  |
| \*1/\*1 (GG) | 2 | 6 | **0.03** | 4 | 0 | **0.1** |
| \*1/\*2 (GA) | 14 | 6 |  | 9 | 5 |  |
| \*2/\*2 (AA) | 4 | 8 |  | 6 | 1 |  |
| \*1/\*1 (GG) | 2 | 6 | **0.1** | 4 | 0 | --- |
| \*1/\*2 (GA)+\*2/\*2 (AA) | 18 | 14 |  | 15 | 6 |  |
| \*1/\*1 (GG)+\*1/\*2 (GA) | 16 | 12 | **0.1** | 13 | 5 | 0.4 |
| \*2/\*2 (AA) | 4 | 8 |  | 6 | 1 |  |
| **UGT2B7** |  |  |  |  |  |  |
| \*1/\*1 (TT) | 2 | 2 | 0.8 | 0 | 1 | **0.04** |
| \*1/\*2 (TC) | 10 | 8 |  | 7 | 4 |  |
| \*2/\*2 (CC) | 8 | 10 |  | 12 | 1 |  |
| \*1/\*1 (TT) | 2 | 2 | 1.0 | 0 | 1 | --- |
| \*1/\*2 (TC)+\*2/\*2 (CC) | 18 | 18 |  | 19 | 5 |  |
| \*1/\*1 (TT)+\*1/\*2 (TC) | 12 | 10 | 0.5 | 7 | 5 | **0.04** |
| \*2/\*2 (CC) | 8 | 10 |  | 12 | 1 |  |
| **UGT2B15** |  |  |  |  |  |  |
| \*1/\*1 (AA) | 1 | 3 | 0.4 | 3 | 0 | --- |
| \*1/\*2 (AC) | 18 | 15 |  | 14 | 6 |  |
| \*2/\*2 (CC) | 1 | 2 |  | 2 | 0 |  |
| \*1/\*1 (AA) | 1 | 3 | **0.2** | 3 | 0 | --- |
| \*1/\*2 (AC)+\*2/\*2 (CC) | 19 | 17 |  | 16 | 6 |  |
| \*1/\*1 (AA)+\*1/\*2 (AC) | 19 | 18 | 0.5 | 17 | 6 | --- |
| \*2/\*2 (CC) | 1 | 2 |  | 2 | 0 |  |
| **Estrogen receptor. TAM therapeutic target** |  |  |  |  |  |  |
| **ESR1 V364E** |  |  |  |  |  |  |
| 364V/364V (TT) | 10 | 16 | **0.09** | 12 | 3 | 0.8 |
| 364V/364E (TA) | 5 | 3 |  | 5 | 2 |  |
| 364E/364E (AA) | 5 | 1 |  | 2 | 1 |  |
| 364V/364V (TT) | 10 | 16 | **0.04** | 12 | 3 | 0.5 |
| 364V/364E (TA) + 364E/364E (AA)  | 10 | 4 |  | 7 | 3 |  |
| 364V/364V (TT)+ 364V/364E (TA) | 15 | 19 | **0.06** | 17 | 5 | 0.6 |
| 364E/364E (AA) | 5 | 1 |  | 2 | 1 |  |

**Table A6a:** Demographic aspects of patients with recurrence and Adverse drug reactions (ADRs: Endometrial cancer, endometrial hyperplasia, and vaginal bleeding) (cases) and without recurrence and ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | *Recurrence* | Endometrial cancer | endometrial hyperplasia |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value*n | *Control* | *Cases* | *p-value* |
|  | n | *Mean±SD* | n | *Mean±SD* | n | Mean±SD | *n* | *Mean±SD* | *n* | Mean±SD | n | *Mean±SD* |
| **Anthropometric Characteristics** |
| Age (years) | 32 | 59±11 | 1 | 59 | 1 | 37 | 58±10 | 0 | - | - | 34 | 58±11 | 3 | 59±3 | 0.8 |
| Weight, (Kg) | 33 | 69±14 | 1 | 78 | 0.5 | 38 | 69±16 | 0 | - | - | 35 | 69±16 | 3 | 62±6 | 0.3 |
| Height, (m) | 32 | 1.55±0.05 | 1 | 1.49 | 0.2 | 37 | 1.54±0.05 | 0 | - | - | 35 | 1.55±0.05 | 2 | 1.44±0.02 | 0.006 |
| BMI (Kg/m2) | 32 | 28±5 | 1 | 35.1 | 0.3 | 37 | 28±6 | 0 | - | - | 35 | 28±6 | 2 | 29±4 | 0.9 |
| **Socio-genetic gradient** |
| **Blood type** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| AB | 0 |  | 0 |  | - | 1 |  | 0 |  | - | 1 |  | 0 |  | 0.8 |
| A | 7 |  | 1 |  | 9 |  | 0 |  | 8 |  | 1 |  |
| B | 1 |  | 0 |  | 1 |  | 0 |  | 1 |  | 0 |  |
| O | 17 |  | 0 |  | 18 |  | 0 |  | 17 |  | 1 |  |
| Number of members in the family | 33 | 3±1 | 1 | 4 | 0.7 | 38 | 3±1 | 0 | - | - | 35 | 3±1 | 3 | 2±1 | 0.3 |
| **Socioeconomic** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <$CLP135,000 (U$ 200) | 5 |  | 0 |  | - | 8 |  | 0 |  | - | 7 |  | 1 |  | 0.8 |
| $CLP135,001-500,000 (U$ 200-750) | 20 |  | 0 |  | 21 |  | 0 |  | 19 |  | 2 |  |
| $CLP 500,001-1,000,000 (U$ >750-1,450) | 8 |  | 1 |  | 9 |  | 0 |  | 9 |  | 0 |  |
| **Risk factor's** |
| Alcoholic Habit Presence | 0 |  | 0 |  | - | 0 |  | 0 |  | - | 0 |  | 0 |  | - |
| Smoking Habit | 8 |  | 0 |  | - | 9 |  | 0 |  | - | 9 |  | 0 |  | - |
| Family history of cancer (any besides BC or OC) | 19 |  | 0 |  | - | 22 |  | 0 |  | - | 20 |  | 2 |  | 0.7 |
| Family History of breast (BC) or ovary cancer (OC) | 11 |  | 0 |  | - | 13 |  | 0 |  | - | 12 |  | 1 |  | 0.9 |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

*Continue Table A6a.*

|  |  |
| --- | --- |
| endometrial hyperplasia | vaginal bleeding |
| *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
| *n* | Mean±SD | n | *Mean±SD* | n | *Mean±SD* | n | Mean±SD |
| **Anthropometric Characteristics** |
| 34 | 58±11 | 3 | 59±3 | 0.8 | 35 | 58±11 | 2 | 61±4 | 0.7 |
| 35 | 69±16 | 3 | 62±6 | 0.3 | 36 | 69±16 | 2 | 60±7 | 0.3 |
| 35 | 1.55±0.05 | 2 | 1.44±0.02 | 0.006 | 35 | 1.54±0..05 | 2 | 1.53±0.09 | 0.6 |
| 35 | 28±6 | 2 | 29±4 | 0.9 | 35 | 29±6 | 2 | 25.9±0.1 | 0.4 |
| **Socio-genetic gradient** |
|  |  |  |  |  |  |  |  |  |  |
| 1 |  | 0 |  | 0.8 | 1 |  | 0 |  | - |
| 8 |  | 1 |  | 9 |  | 0 |  |
| 1 |  | 0 |  | 1 |  | 0 |  |
| 17 |  | 1 |  | 18 |  | 0 |  |
| 35 | 3±1 | 3 | 2±1 | 0.3 | 36 | 3±1 | 2 | 2±2 | 0.3 |
|  |  |  |  |  |  |  |  |  |  |
| 7 |  | 1 |  | 0.8 | 7 |  | 1 |  | 0.4 |
| 19 |  | 2 |  | 20 |  | 1 |  |
| 9 |  | 0 |  | 9 |  | 0 |  |
| **Risk factor's** |
| 0 |  | 0 |  | - | 0 |  | 0 |  | - |
| 9 |  | 0 |  | - | 8 |  | 1 |  | 0.4 |
| 20 |  | 2 |  | 0.7 | 21 |  | 1 |  | 0.8 |
| 12 |  | 1 |  | 0.9 | 12 |  | 1 |  | 0.6 |

**Table A6b:** Demographic aspects of patients with ADRs (Phlebitis, Headache, Nausea, and hot flash) (cases) and without ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |
| --- | --- | --- |
|  | Phlebitis | Headache |
|  | *Control* | *Cases* | *p-value*n | *Control* | *Cases* | *p-value* |
|  | *n* | Mean±SD | n | *Mean±SD* | n | *Mean±SD* | n | Mean±SD |
| **Anthropometric Characteristics** |
| Age (years) | 36 | 58±11 | 1 | 49 | 0.3 | 35 | 59±10 | 2 | 43±2 | 0.01 |
| Weight, (Kg) | 37 | 69±16 | 1 | 60 | 0.5 | 36 | 68±14 | 2 | 78±45 | 0.4 |
| Height, (m) | 36 | 1.54±0.05 | 1 | 1.61 | 0.2 | 35 | 1.54±0.05 | 2 | 0.04 | 1.54±0.05 |
| BMI (Kg/m2) | 36 | 29±6 | 1 | 23.1 | 0.2 | 35 | 28±5 | 2 | 31±16 | 0.5 |
| **Socio-genetic gradient** |
| Blood type |  |  |  |  |  |  |  |  |  |  |
| AB | 1 |  | 0 |  | - | 1 |  | 0 |  | - |
| A | 8 |  | 1 |  | 9 |  | 0 |  |
| B | 1 |  | 0 |  | 1 |  | 0 |  |
| O | 18 |  | 0 |  | 17 |  | 1 |  |
| Number of members in the family | 37 | 3±1 | 1 | 3 | 0.7 | 36 | 3±1 | 2 | 4±3 | 0.3 |
| Socioeconomic |  |  |  |  |  |  |  |  |  |  |
| <$CLP135,000 (U$ 200) | 7 |  | 0 |  | - | 7 |  | 1 |  | 0.4 |
| $CLP135,001-500,000 (U$ 200-750) | 21 |  | 0 |  | 20 |  | 1 |  |
| $CLP 500,001-1,000,000 (U$ >750-1,450) | 9 |  | 0 |  | 9 |  | 0 |  |
| **Risk factor's** |
| Alcoholic Habit Presence | 0 |  | 0 |  | - | 0 |  | 0 |  |
| Smoking Habit | 9 |  | 0 |  | - | 8 |  | 1 |  |
| Family history of cancer (any besides BC or OC) | 22 |  | 0 |  | - | 20 |  | 2 |  |
| Family History of breast (BC) or ovary cancer (OC) | 13 |  | 0 |  | - | 11 |  | 2 |  |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

*Continue Table A6b*

|  |  |
| --- | --- |
| Nausea | hot flash |
| *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
| n | Mean±SD | *n* | Mean±SD | *n* | Mean±SD | n | *Mean±SD* |
|  |
| 34 | 59±11 | 3 | 53±9 | 0.3 | 11 | 62±12 | 26 | 57±10 | 0.2 |
| 35 | 69±16 | 3 | 65±19 | 0.6 | 12 | 65±17 | 26 | 70±15 | 0.3 |
| 34 | 1.55±0.05 | 3 | 1.50±0.07 | 0.1 | 12 | 1.54±0.04 | 25 | 1.54±0.06 | 0.8 |
| 34 | 28±6 | 3 | 29±8 | 0.9 | 12 | 27±7 | 25 | 29±5 | 0.2 |
|  |
|  |  |  |  |  |  |  |  |  |  |
| 1 |  | 0 |  | 0.8 | 0 |  | 1 |  | 0.4 |
| 8 |  | 1 |  | 4 |  | 5 |  |
| 1 |  | 0 |  | 0 |  | 1 |  |
| 17 |  | 1 |  | 5 |  | 13 |  |
| 35 | 3±1 | 3 | 3±1 | 0.6 | 12 | 3±1 | 26 | 3±1 | 0.3 |
|  |  |  |  |  |  |  |  |  |  |
| 8 |  | 0 |  | - | 4 |  | 4 |  | 0.4 |
| 18 |  | 3 |  | 5 |  | 16 |  |
| 9 |  | 0 |  | 3 |  | 6 |  |
|  |
| 0 |  | 0 |  | - | 0 |  | 0 |  | - |
| 8 |  | 1 |  | 0.6 | 2 |  | 7 |  | 0.4 |
| 21 |  | 1 |  | 0.3 | 8 |  | 14 |  | 0.4 |
| 12 |  | 1 |  | 0..9 | 3 |  | 10 |  | 0.4 |

**Table A6c:** Demographic aspects of patients with ADRs (Cramps, Bone pain, and Urticaria) (cases) and without ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |
| --- | --- | --- |
|  | Cramps | Bone pain |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |  |
|  | *n* | Mean±SD | n | *Mean±SD* |  | *Mean±SD* |  | *Mean±SD* |  |  |
| **Anthropometric Characteristics** |
| Age (years) | 30 | 58±11 | 7 | 60±9 | 0.6 | 29 | 59±10 | 8 | 54±10 | 0.1 |  |  |
| Weight, (Kg) | 31 | 69±16 | 7 | 68±13 | 0.9 | 30 | 68±16 | 8 | 70±14 | 0.7 |  |  |
| Height, (m) | 30 | 1.54±0.05 | 7 | 1.55±0.06 | 0..6 | 29 | 1.53±0.05 | 8 | 1.58±0.05 | 0.03 |  |  |
| BMI (Kg/m2) | 30 | 29±6 | 7 | 28±5 | 0.8 | 29 | 29±6 | 8 | 28±4 | 0.7 |  |  |
| **Socio-genetic gradient** |
| Blood type |  |  |  |  |  |  |  |  |  |  |  |  |
| AB | 1 |  | 0 |  | 0.6 | 1 |  | 0 |  | 0.2 |  |  |
| A | 8 |  | 1 |  | 5 |  | 4 |  |  |
| B | 1 |  | 0 |  | 1 |  | 0 |  |  |
| O | 14 |  | 4 |  | 15 |  | 3 |  |  |
| Number of members in the family | 31 | 3±1 | 7 | 2±1 | 0.09 | 30 | 3±1 | 8 | 2.5±0.9 | 0.05 |  |  |
| Socioeconomic |  |  |  |  |  |  |  |  |  |  |  |  |
| <$CLP135,000 (U$ 200) | 4 |  | 4 |  | 0.05 | 6 |  | 2 |  | 0.9 |  |  |
| $CLP135,001-500,000 (U$ 200-750) | 19 |  | 2 |  | 17 |  | 4 |  |  |
| $CLP 500,001-1,000,000 (U$ >750-1,450) | 8 |  | 1 |  | 7 |  | 2 |  |  |
| **Risk factor's** |
| Alcoholic Habit Presence | 0 |  | 0 |  | - | 0 |  | 0 |  | - |  |  |
| Smoking Habit | 8 |  | 1 |  | 0.4 | 7 |  | 2 |  | 0.9 |  |  |
| Family history of cancer (any besides BC or OC) | 17 |  | 5 |  | 0.4 | 18 |  | 4 |  | 0.6 |  |  |
| Family History of breast (BC) or ovary cancer (OC) | 9 |  | 4 |  | 0.1 | 9 |  | 4 |  | 0.2 |  |  |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

*Continue Table A6c*

|  |
| --- |
| Urticaria |
| *Control* | *Cases* | *p-value* |
|  | *Mean±SD* |  | *Mean±SD* |
|  |
| 37 | 58±10 | 0 | - | - |
| 38 | 69±16 | 0 | - | - |
| 37 | 1.54±0.05 | 0 | - | - |
| 37 | 28±6 | 0 | - | - |
|  |
|  |  |  |  |  |
| 1 |  | 0 |  | - |
| 9 |  | 0 |  |
| 1 |  | 0 |  |
| 18 |  | 0 |  |
| 38 | 3±1 | 0 | - | - |
|  |  |  |  |  |
| 8 |  | 0 |  | - |
| 21 |  | 0 |  |
| 9 |  | 0 |  |
|  |
| 0 |  | 0 |  | - |
| 9 |  | 0 |  | - |
| 22 |  | 0 |  | - |
| 13 |  | 0 |  | - |

**Table A7a:** Gynecological and Pathological features of patients with recurrence and Adverse drug reactions (ADRs: Endometrial cancer, endometrial hyperplasia, and vaginal bleeding) (cases) and without recurrence and ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |
| --- | --- | --- |
|  | *Recurrence* | Endometrial cancer |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
|  | n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD |
| Gynecological Characteristics |
| Menarche age (years) | 33 | 12±1 | 1 | 9 | - | 38 | 12±2 | 0 | - | - |
| Number of Gestations | 33 | 3±2 | 1 | 2 | 0.5 | 38 | 3±2 | 0 | - | - |
| Number of deliveries | 33 | 2±1 | 1 | 2 | 0.7 | 38 | 2±1 | 0 | - | - |
| Number of Abortions | 33 | 0.6±0.9 | 1 | 0 | - | 38 | 0.5±0.8 | 0 | - | - |
| Breastfeeding time (months) | 29 | 24±26 | 0 | - | - | 33 | 26±27 | 0 | - | - |
| Oral Contraceptive Treatment (months) | 33 | 55±85 | 1 | 0 | - | 38 | 49±81 | 0 | - | - |
| Menopausal status |  |  |  |  |  |  |  |  |  |  |
| Premenopausal | 11 |  | 0 |  | - | 13 |  | 0 |  | - |
| Postmenopausal | 22 |  | 1 |  | 25 |  | 0 |  |
| Treatment with HRT for menopause (months) | 32 | 3±9 | 1 | 60 | - | 37 | 4±13 | 0 | - | - |
| Pathological Features |
| Age of diagnosis (years) | 33 | 53±11 | 1 | 49 | 0.6 | 38 | 53±11 | 0 | - | - |
| Cancer stage at diagnosis |  |  |  |  |  |  |  |  |  |  |
| I | 12 |  | 1 |  | - | 14 |  | 0 |  | - |
| II | 17 |  | 0 |  | 20 |  | 0 |  |
| III | 4 |  | 0 |  | 4 |  | 0 |  |
| Tumor Histology |  |  |  |  |  |  |  |  |  |  |
| Ductal carcinoma in situ | 1 |  | 0 |  | - | 1 |  | 0 |  | - |
| Invasive Ductal Carcinoma  | 29 |  | 1 |  | 34 |  | 0 |  |
| Invasive Lobular Carcinoma  | 1 |  | 0 |  | 1 |  | 0 |  |
| Others, (IBC, IPC, etc.) | 2 |  | 0 |  | 2 |  | 0 |  |
| Cell Differentiation Degree |  |  |  |  |  |  |  |  |  |  |
| G1 | 7 |  | 0 |  | - | 8 |  | 0 |  | - |
| G2 | 17 |  | 0 |  | 19 |  | 0 |  |
| G3 | 5 |  | 0 |  | 6 |  | 0 |  |
| Treatment before to TAM |  |  |  |  |  |  |  |  |  |  |
| Surgery | 2 |  | 0 |  | - | 3 |  | 0 |  | - |
| Surgery + radiotherapy | 7 |  | 0 |  | 8 |  | 0 |  |
| Surgery + chemotherapy  | 1 |  | 0 |  | 2 |  | 0 |  |
| Surgery + chemotherapy + radiotherapy | 5 |  | 0 |  | 6 |  | 0 |  |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

*Continue Table A7a*

|  |  |
| --- | --- |
| endometrial hyperplasia | vaginal bleeding |
| *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
| n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD |
|  |
| 35 | 12±2 | 3 | 10.6±0.5 | 0.03 | 36 | 12±2 | 2 | 11.5±0.7 | 0.3 |
| 35 | 3±1 | 3 | 3±5 | 0.9 | 36 | 3±2 | 2 | 0.5±0.7 | 0.02 |
| 35 | 2±1 | 3 | 2±3 | 0.6 | 36 | 2±1 | 2 | 0 | - |
| 35 | 0.5±0.8 | 3 | 1±1 | 0.4 | 36 | 0.5±0.9 | 2 | 0.5±0.7 | 0.8 |
| 30 | 25±26 | 3 | 28±48 | 0.9 | 31 | 27±27 | 2 | 0 | - |
| 35 | 53±83 | 3 | 0.3±0.5 | 0.05 | 36 | 52±83 | 2 | 0.5±0.7 | 0.1 |
|  |  |  |  |  |  |  |  |  |  |
| 12 |  | 1 |  | 0.9 | 13 |  | 0 |  | - |
| 23 |  | 2 |  | 23 |  | 2 |  |
| 34 | 3±12 | 3 | 12±20 | 0.3 | 35 | 4±13 | 2 | 0 | - |
|  |
| 35 | 53±11 | 3 | 53±8 | 0.9 | 36 | 53±11 | 2 | 58±7 | 0.5 |
|  |  |  |  |  |  |  |  |  |  |
| 12 |  | 2 |  | 0.3 | 13 |  | 1 |  | 0.7 |
| 19 |  | 1 |  | 19 |  | 1 |  |
| 4 |  | 0 |  | 4 |  | 0 |  |
|  |  |  |  |  |  |  |  |  |  |
| 1 |  | 0 |  | 0.2 | 1 |  | 0 |  | - |
| 32 |  | 2 |  | 32 |  | 2 |  |
| 1 |  | 0 |  | 1 |  | 0 |  |
| 1 |  | 1 |  | 2 |  | 0 |  |
|  |  |  |  |  |  |  |  |  |  |
| 8 |  | 0 |  | - | 8 |  | 0 |  | **-** |
| 17 |  | 2 |  | 17 |  | 2 |  |
| 6 |  | 0 |  | 6 |  | 0 |  |
|  |  |  |  |  |  |  |  |  |  |
| 3 |  | 0 |  | - | 3 |  | 0 |  | **-** |
| 6 |  | 2 |  | 7 |  | 1 |  |
| 2 |  | 0 |  | 2 |  | 0 |  |
| 6 |  | 0 |  | 6 |  | 0 |  |

**Table A7b:** Gynecological and Pathological features of patients with ADRs (Phlebitis, Headache, Nausea, and hot flash) (cases) and without ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |
| --- | --- | --- |
|  | Phlebitis | Headache |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
|  | n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD |
| Gynecological Characteristics |
| Menarche age (years) | 37 | 12±2 | 1 | 16 | **0.1** | 36 | 12±2 | 2 | 13.5±0.7 | 0.6 |
| Number of Gestations | 37 | 3±2 | 1 | 1 | 0.2 | 36 | 2±2 | 2 | 5 | 0.2 |
| Number of deliveries | 37 | 2±1 | 1 | 1 | 0.3 | 36 | 2±1 | 2 | 3.5±0.7 | 0.4 |
| Number of Abortions | 37 | 0.5±0.8 | 1 | 0 | **-** | 36 | 0.5±0.8 | 2 | 1.5±0.7 | 0.2 |
| Breastfeeding time (months) | 32 | 26±28 | 1 | 6 | 0.3 | 31 | 25±28 | 2 | 28±27 | 0.9 |
| Oral Contraceptive Treatment (months) | 37 | 49±82 | 1 | 36 | 0.8 | 36 | 51±83 | 2 | 19±23 | 0.5 |
| Menopausal status |  |  |  |  |  |  |  |  |  |  |
| Premenopausal | 12 |  | 1 |  | **-** | 11 |  | 2 |  | - |
| Postmenopausal | 25 |  | 0 |  | 25 |  | 0 |  |
| Treatment with HRT for menopause (months) | 36 | 4±13 | 1 | 0 | - | 35 | 4±13 | 2 | 0 | - |
| Pathological Features |
| Age of diagnosis (years) | 37 | 54±11 | 1 | 49 | 0.6 | 36 | 54±10 | 2 | 38±7 | 0.02 |
| Cancer stage at diagnosis |  |  |  |  |  |  |  |  |  |  |
| I | 14 |  | 0 |  | - | 13 |  | 1 |  | 0.7 |
| II | 19 |  | 1 |  | 19 |  | 1 |  |
| III | 4 |  | 0 |  | 4 |  | 0 |  |
| Tumor Histology |  |  |  |  |  |  |  |  |  |  |
| Ductal carcinoma in situ | 1 |  | 0 |  | - | 1 |  | 0 |  | - |
| Invasive Ductal Carcinoma  | 33 |  | 1 |  | 32 |  | 2 |  |
| Invasive Lobular Carcinoma  | 1 |  | 0 |  | 1 |  | 0 |  |
| Others, (IBC, IPC, etc.) | 2 |  | 0 |  | 2 |  | 0 |  |
| Cell Differentiation Degree |  |  |  |  |  |  |  |  |  |  |
| G1 | 7 |  | 1 |  | - | 8 |  | 0 |  | - |
| G2 | 19 |  | 0 |  | 17 |  | 2 |  |
| G3 | 6 |  | 0 |  | 6 |  | 0 |  |
| Treatment before to TAM |  |  |  |  |  |  |  |  |  |  |
| Surgery | 3 |  | 0 |  | **-** | 3 |  | 0 |  | **-** |
| Surgery + radiotherapy | 8 |  | 0 |  | 8 |  | 0 |  |
| Surgery + chemotherapy  | 2 |  | 0 |  | 1 |  | 1 |  |
| Surgery + chemotherapy + radiotherapy | 5 |  | 1 |  | 6 |  | 0 |  |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

Continue Table A7b

|  |  |
| --- | --- |
| Nausea | hot flash |
| *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
| n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD |
|  |
| 35 | 12±2 | 3 | 12±2 | **0.9** | 12 | 13±1 | 26 | 12±2 | 0.4 |
| 35 | 2±1 | 3 | 5±3 | 0.03 | 12 | 3±2 | 26 | 2±2 | 0.4 |
| 35 | 2±1 | 3 | 4±1 | 0.1 | 12 | 2±2 | 26 | 2±1 | 0.5 |
| 35 | 0.4±0.7 | 3 | 1±1 | 0.06 | 12 | 1±1 | 26 | 0.5±0.7 | 0.6 |
| 30 | 24±26 | 3 | 43±37 | 0.2 | 10 | 16±18 | 23 | 30±30 | 0.1 |
| 35 | 52±84 | 3 | 20±18 | 0.4 | 12 | 36±65 | 26 | 55±88 | 0.4 |
|  |  |  |  |  |  |  |  |  |  |
| 11 |  | 2 |  | 0.2 | 3 |  | 10 |  | 0.4 |
| 24 |  | 1 |  | 9 |  | 16 |  |
| 34 | 4±13 | 3 | 0 | - | 12 | 8±19 | 25 | 2±8 | 0.2 |
|  |
| 35 | 54±11 | 3 | 45±11 | 0.1 | 12 | 56±12 | 26 | 52±10 | 0.3 |
|  |  |  |  |  |  |  |  |  |  |
| 13 |  | 1 |  | 0.7 | 8 |  | 6 |  | 0.02 |
| 18 |  | 2 |  | 4 |  | 16 |  |
| 4 |  | 0 |  | 0 |  | 4 |  |
|  |  |  |  |  |  |  |  |  |  |
| 1 |  | 0 |  | - | 1 |  | 0 |  | - |
| 31 |  | 3 |  | 10 |  | 24 |  |
| 1 |  | 0 |  | 1 |  | 0 |  |
| 2 |  | 0 |  | 0 |  | 2 |  |
|  |  |  |  |  |  |  |  |  |  |
| 8 |  | 0 |  | - | 2 |  | 6 |  | 0.9 |
| 16 |  | 3 |  | 5 |  | 14 |  |
| 6 |  | 0 |  | 2 |  | 4 |  |
|  |  |  |  |  |  |  |  |  |  |
| 3 |  | 0 |  | - | 0 |  | 3 |  | - |
| 8 |  | 0 |  | 4 |  | 4 |  |
| 2 |  | 0 |  | 2 |  | 0 |  |
| 6 |  | 0 |  | 1 |  | 5 |  |

**Table A7c:** Gynecological and Pathological features of patients with ADRs (Cramps, Bone pain, and Urticaria) (cases) and without ADRs (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Cramps | Bone pain | Urticaria |
|  | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* | *Control* | *Cases* | *p-value* |
|  | n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD | n | Mean±SD |
| Gynecological Characteristics |
| Menarche age (years) | 31 | 12±2 | 7 | 12±1 | **0.8** | 30 | 12±2 | 8 | 13±1 | 0.1 | 38 | 12±2 | 0 | - | **-** |
| Number of Gestations | 31 | 3±2 | 7 | 2±2 | 0.5 | 30 | 3±2 | 8 | 2±1 | 0.3 | 38 | 3±2 | 0 | - | - |
| Number of deliveries | 31 | 2±1 | 7 | 2±2 | 0.7 | 30 | 2±1 | 8 | 1±1 | 0.2 | 38 | 2±1 | 0 | - | **-** |
| Number of Abortions | 31 | 0.6±0.9 | 7 | 0.2±0.4 | **0.2** | 30 | 0.6±0.9 | 8 | 0.5±0.7 | 0.7 | 38 | 0.5±0.8 | 0 | - | - |
| Breastfeeding time (months) | 26 | 26±26 | 7 | 24±33 | 0.8 | 26 | 28±28 | 7 | 16±22 | 0.2 | 33 | 26±27 | 0 | - | - |
| Oral Contraceptive Treatment (months) | 31 | 53±82 | 7 | 31±81 | 0.4 | 30 | 51±87 | 8 | 43±60 | **0.8** | 38 | 49±81 | 0 | - | **-** |
| Menopausal status |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Premenopausal | 12 |  | 1 |  | **0.1** | 9 |  | 4 |  | **0.2** | 13 |  | 0 |  | - |
| Postmenopausal | 19 |  | 6 |  | 21 |  | 4 |  | 25 |  | 0 |  |
| Treatment with HRT for menopause (months) | 30 | 4±13 | 7 | 5±13 | 0.8 | 29 | 5±14 | 8 | 0 | - | 37 | 4±13 | 0 | - | - |
| Pathological Features |
| Age of diagnosis (years) | 31 | 53±11 | 7 | 57±9 | 0.4 | 30 | 55±10 | 8 | 48±11 | 0.4 | 38 | 53±11 | 0 | - | - |
| Cancer stage at diagnosis |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| I | 10 |  | 4 |  | 0.04 | 12 |  | 2 |  | 0.7 | 14 |  | 0 |  | **-** |
| II | 19 |  | 1 |  | 15 |  | 5 |  | 20 |  | 0 |  |
| III | 2 |  | 2 |  | 3 |  | 1 |  | 4 |  | 0 |  |
| Tumor Histology |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ductal carcinoma in situ | 1 |  | 0 |  | 0.4 | 1 |  | 0 |  | 0.5 | 1 |  | 0 |  | - |
| Invasive Ductal Carcinoma  | 28 |  | 6 |  | 27 |  | 7 |  | 34 |  | 0 |  |
| Invasive Lobular Carcinoma  | 1 |  | 0 |  | 1 |  | 0 |  | 1 |  | 0 |  |
| Others, (IBC, IPC, etc.) | 1 |  | 1 |  | 1 |  | 1 |  | 2 |  | 0 |  |
| Cell Differentiation Degree |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| G1 | 7 |  | 1 |  | 0.1 | 5 |  | 3 |  | 0.3 | 8 |  | 0 |  | - |
| G2 | 17 |  | 2 |  | 15 |  | 4 |  | 19 |  | 0 |  |
| G3 | 3 |  | 3 |  | 6 |  | 0 |  | 6 |  | 0 |  |
| Treatment before to TAM |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Surgery | 2 |  | 1 |  | **0.7** | 3 |  | 0 |  | **-** | 3 |  | 0 |  | - |
| Surgery + radiotherapy | 6 |  | 2 |  | 8 |  | 0 |  | 8 |  | 0 |  |
| Surgery + chemotherapy  | 1 |  | 1 |  | 2 |  | 0 |  | 2 |  | 0 |  |
| Surgery + chemotherapy + radiotherapy | 6 |  | 0 |  | 5 |  | 1 |  | 6 |  | 0 |  |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

**Table SVIIIa:** Genotypic and allelic frequencies of CYP2D6\*4 (rs3892097), CYP3A4\*1B (rs2740574), CYP3A5\*3 (rs776746), SULT1A1\*2 (rs9282861), UGT2B7\*2 (rs7439366), UGT2B15\*2 (rs1902023), and ESR1 V364E (rs121913044) polymorphisms in patients with recurrence and Adverse drug reactions (ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, and phlebitis) (cases) and without recurrence and adverse drug reactions (ADRs) (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Recurrence | Endometrial cancer | endometrial hyperplasia |
|  | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value |
| **Enzymes involved in the activation of TAM** |
| **CYP2D6** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 26 | 1 | - | 31 | 0 | - | 29 | 2 | 0.5 |
| \*1/\*4 (GA) | 7 | 0 | 7 | 0 | 6 | 1 |
| \*4/\*4 (AA) | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A4** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 28 | 1 | - | 33 | 0 | - | 30 | 3 | - |
| \*1/\*1B (AG) | 5 | 0 | 5 | 0 | 5 | 0 |
| \*1B/\*1B (GG) | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A5** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 0 | 0 | - | 0 | 0 | - | 0 | 0 | - |
| \*1/\*3 (AG) | 16 | 1 | 18 | 0 | 16 | 2 |
| \*3/\*3 (GG) | 17 | 0 | 20 | 0 | 19 | 1 |
| **Enzymes involved in the elimination of TAM and its metabolites** |
| **SULT1A1** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 7 | 0 | - | 8 | 0 | - | 7 | 1 | 0.8 |
| \*1/\*2 (GA) | 15 | 1 | 18 | 0 | 17 | 1 |
| \*2/\*2 (AA) | 11 | 0 | 12 | 0 | 11 | 1 |
| \*1/\*1 (GG) | 7 | 0 | - | 8 | 0 | - | 7 | 1 | 0.6 |
| \*1/\*2 (GA)+\*2/\*2 (AA) | 26 | 1 | 30 | 0 | 28 | 2 |
| \*1/\*1 (GG)+\*1/\*2 (GA) | 22 | 1 | - | 26 | 0 | - | 24 | 2 | 0.9 |
| \*2/\*2 (AA) | 11 | 0 | 12 | 0 | 11 | 1 |
| **UGT2B7** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (TT) | 2 | 0 | - | 4 | 0 | - | 4 | 0 | - |
| \*1/\*2 (TC) | 15 | 0 | 17 | 0 | 16 | 1 |
| \*2/\*2 (CC) | 16 | 1 | 17 | 0 | 15 | 2 |
| \*1/\*1 (TT) | 2 | 0 | - | 4 | 0 | - | 4 | 0 | - |
| \*1/\*2 (TC)+\*2/\*2 (CC) | 31 | 1 | 34 | 0 | 31 | 3 |
| \*1/\*1 (TT)+\*1/\*2 (TC) | 17 | 0 | - | 21 | 0 | - | 20 | 1 | 0.4 |
| \*2/\*2 (CC) | 16 | 1 | 17 | 0 | 15 | 2 |
| **UGT2B15** |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 3 | 1 | - | 4 | 0 | - | 4 | 0 | - |
| \*1/\*2 (AC) | 28 | 0 | 32 | 0 | 30 | 2 |
| \*2/\*2 (CC) | 2 | 0 | 2 | 0 | 1 | 1 |
| \*1/\*1 (AA) | 3 | 1 | - | 4 | 0 | - | 4 | 0 | - |
| \*1/\*2 (AC)+\*2/\*2 (CC) | 30 | 0 | 34 | 0 | 31 | 3 |
| \*1/\*1 (AA)+\*1/\*2 (AC) | 31 | 1 | - | 36 | 0 | - | 34 | 2 | 0.09 |
| \*2/\*2 (CC) | 2 | 0 | 2 | 0 | 1 | 1 |
| **Estrogen receptor. TAM therapeutic target** |
| **ESR1 V364E** |  |  |  |  |  |  |  |  |  |
| 364V/364V (TT) | 22 | 1 | - | 25 | 0 | - | 23 | 2 | 0.5 |
| 364V/364E (TA) | 6 | 0 | 7 | 0 | 7 | 0 |
| 364E/364E (AA) | 5 | 0 | 6 | 0 | 5 | 1 |
| 364V/364V (TT) | 22 | 1 | - | 25 | 0 | - | 23 | 2 | 0.9 |
| 364V/364E (TA) + 364E/364E (AA)  | 11 | 0 | 13 | 0 | 12 | 1 |
| 364V/364V (TT)+ 364V/364E (TA) | 28 | 1 | - | 32 | 0 | - | 30 | 2 | 0.4 |
| 364E/364E (AA) | 5 | 0 | 6 | 0 | 5 | 1 |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

Continue Table A8a

|  |  |
| --- | --- |
| vaginal bleeding | Phlebitis |
| Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value |
|  |
|  |  |  |  |  |  |
| 30 | 1 | 0.2 | 30 | 1 | - |
| 6 | 1 | 7 | 0 |
| 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |
| 31 | 2 | - | 32 | 1 | - |
| 5 | 0 | 5 | 0 |
| 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |
| 0 | 0 | 0.9 | 0 | 0 | **-** |
| 17 | 1 | 18 | 0 |
| 19 | 1 | 19 | 1 |
|  |
|  |  |  |  |  |  |
| 8 | 0 | - | 8 | 0 | **-** |
| 18 | 0 | 17 | 1 |
| 10 | 2 | 12 | 0 |
| 8 | 0 | - | 8 | 0 | - |
| 28 | 2 | 29 | 1 |
| 26 | 0 | - | 25 | 1 | - |
| 10 | 2 | 12 | 0 |
|  |  |  |  |  |  |
| 4 | 0 | - | 3 | 1 | **-** |
| 16 | 1 | 17 | 0 |
| 16 | 1 | 17 | 0 |
| 4 | 0 | - | 3 | 1 | - |
| 32 | 2 | 34 | 0 |
| 20 | 1 | 0.8 | 20 | 1 | **-** |
| 16 | 1 | 17 | 0 |
|  |  |  |  |  |  |
| 4 | 0 | - | 4 | 0 | - |
| 30 | 2 | 31 | 1 |
| 2 | 0 | 2 | 0 |
| 4 | 0 | - | 4 | 0 | - |
| 32 | 2 | 33 | 1 |
| 34 | 2 | - | 35 | 1 | - |
| 2 | 0 | 2 | 0 |
|  |
|  |  |  |  |  |  |
| 24 | 1 | 0.3 | 25 | 0 | - |
| 7 | 0 | 6 | 1 |
| 5 | 1 | 6 | 0 |
| 24 | 1 | 0.6 | 25 | 0 | - |
| 12 | 1 | 12 | 1 |
| 31 | 1 | 0.2 | 31 | 1 | - |
| 5 | 1 | 6 | 0 |

**Table A8b:** Genotypic and allelic frequencies of CYP2D6\*4 (rs3892097), CYP3A4\*1B (rs2740574), CYP3A5\*3 (rs776746), SULT1A1\*2 (rs9282861), UGT2B7\*2 (rs7439366), UGT2B15\*2 (rs1902023), and ESR1 V364E (rs121913044) polymorphisms in patients with Adverse drug reactions (ADRs: Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria) (cases) and without Adverse drug reactions (ADRs) (controls) for the study and bivariable logistic regression analysis.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Headache | Nausea | hot flash | Cramps | Bone pain | Urticaria |
|  | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value | Control (n) | Cases (n) | p-value |
| **Enzymes involved in the activation of TAM** |
| **CYP2D6** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 29 | 2 | - | 29 | 2 | 0.5 | 10 | 21 | 0.8 | 25 | 6 | 0.7 | 23 | 8 | - | 31 | 0 | - |
| \*1/\*4 (GA) | 7 | 0 | 6 | 1 | 2 | 5 | 6 | 1 | 7 | 0 | 7 | 0 |
| \*4/\*4 (AA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A4** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 31 | 2 | - | 30 | 3 | - | 12 | 21 | - | 27 | 6 | 0.9 | 27 | 6 | 0.2 | 33 | 0 | - |
| \*1/\*1B (AG) | 5 | 0 | 5 | 0 | 0 | 5 | 4 | 1 | 3 | 2 | 5 | 0 |
| \*1B/\*1B (GG) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **CYP3A5** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 0 | 0 | - | 0 | 0 | 0.6 | 0 | 0 | 0.6 | 0 | 0 | 0.5 | 0 | 0 | 0.5 | 0 | 0 | - |
| \*1/\*3 (AG) | 18 | 0 | 17 | 1 | 5 | 13 | 14 | 4 | 15 | 3 | 18 | 0 |
| \*3/\*3 (GG) | 18 | 2 | 18 | 2 | 7 | 13 | 17 | 3 | 15 | 5 | 20 | 0 |
| **Enzymes involved in the elimination of TAM and its metabolites** |
| **SULT1A1** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (GG) | 7 | 1 | 0.7 | 8 | 0 | - | 2 | 6 | 0.6 | 5 | 3 | 0.2 | 5 | 3 | 0.2 | 8 | 0 | - |
| \*1/\*2 (GA) | 18 | 0 | 17 | 1 | 5 | 13 | 15 | 3 | 16 | 2 | 18 | 0 |
| \*2/\*2 (AA) | 11 | 1 | 10 | 2 | 5 | 7 | 11 | 1 | 9 | 3 | 12 | 0 |
| \*1/\*1 (GG) | 7 | 1 | 0.3 | 8 | 0 | - | 2 | 6 | 0.6 | 5 | 3 | 0.1 | 5 | 3 | 0.2 | 8 | 0 | - |
| \*1/\*2 (GA)+\*2/\*2 (AA) | 29 | 1 | 27 | 3 | 10 | 20 | 26 | 4 | 25 | 5 | 30 | 0 |
| \*1/\*1 (GG)+\*1/\*2 (GA) | 25 | 1 | 0.5 | 25 | 1 | 0.1 | 7 | 19 | 0.3 | 20 | 6 | 0.2 | 21 | 5 | 0.6 | 26 | 0 | - |
| \*2/\*2 (AA) | 11 | 1 | 10 | 2 | 5 | 7 | 11 | 1 | 9 | 3 | 12 | 0 |
| **UGT2B7** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (TT) | 3 | 1 | 0.2 | 4 | 0 | - | 2 | 2 | 0.04 | 4 | 0 | - | 2 | 2 | 0.3 | 4 | 0 | - |
| \*1/\*2 (TC) | 17 | 0 | 17 | 0 | 2 | 15 | 12 | 5 | 14 | 3 | 17 | 0 |
| \*2/\*2 (CC) | 16 | 1 | 14 | 3 | 8 | 9 | 15 | 2 | 14 | 3 | 17 | 0 |
| \*1/\*1 (TT) | 3 | 1 | 0.1 | 4 | 0 | - | 2 | 2 | 0.4 | 4 | 0 | - | 2 | 2 | 0.1 | 4 | 0 | - |
| \*1/\*2 (TC)+\*2/\*2 (CC) | 33 | 1 | 31 | 3 | 10 | 24 | 27 | 7 | 28 | 6 | 34 | 0 |
| \*1/\*1 (TT)+\*1/\*2 (TC) | 20 | 1 | 0.8 | 21 | 0 | - | 4 | 17 | 0.06 | 16 | 5 | 0.3 | 16 | 5 | 0.6 | 21 | 0 | - |
| \*2/\*2 (CC) | 16 | 1 | 14 | 3 | 8 | 9 | 15 | 2 | 14 | 3 | 17 | 0 |
| **UGT2B15** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| \*1/\*1 (AA) | 4 | 0 | - | 4 | 0 | - | 2 | 2 | 0.4 | 2 | 2 | 0.1 | 2 | 2 | 0.1 | 4 | 0 | - |
| \*1/\*2 (AC) | 30 | 2 | 30 | 2 | 10 | 22 | 28 | 4 | 26 | 6 | 32 | 0 |
| \*2/\*2 (CC) | 2 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 2 | 0 | 2 | 0 |
| \*1/\*1 (AA) | 4 | 0 | - | 4 | 0 | - | 2 | 2 | 0.4 | 2 | 2 | 0.1 | 2 | 2 | 0.1 | 4 | 0 | - |
| \*1/\*2 (AC)+\*2/\*2 (CC) | 32 | 2 | 31 | 3 | 10 | 24 | 29 | 5 | 28 | 6 | 34 | 0 |
| \*1/\*1 (AA)+\*1/\*2 (AC) | 34 | 2 | - | 34 | 2 | 0.09 | 12 | 24 | - | 30 | 6 | 0.2 | 28 | 8 | - | 36 | 0 | - |
| \*2/\*2 (CC) | 2 | 0 | 1 | 1 | 0 | 2 | 1 | 1 | 2 | 0 | 2 | 0 |
| **Estrogen receptor. TAM therapeutic target** |
| **ESR1 V364E** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 364V/364V (TT) | 23 | 2 | - | 22 | 3 | - | 7 | 18 | 0.2 | 21 | 4 | 0.7 | 18 | 7 | 0.4 | 27 | 0 | - |
| 364V/364E (TA) | 7 | 0 | 7 | 0 | 4 | 3 | 5 | 2 | 6 | 1 | 7 | 0 |
| 364E/364E (AA) | 6 | 0 | 6 | 0 | 1 | 5 | 5 | 1 | 6 | 0 | 6 | 0 |
| 364V/364V (TT) | 23 | 2 | - | 22 | 3 | - | 7 | 18 | 0.5 | 21 | 4 | 0.5 | 18 | 7 | 0.1 | 25 | 0 | - |
| 364V/364E (TA) + 364E/364E (AA)  | 13 | 0 | 13 | 0 | 5 | 8 | 10 | 3 | 12 | 1 | 13 | 0 |
| 364V/364V (TT)+ 364V/364E (TA) | 30 | 2 | - | 29 | 3 | - | 11 | 21 | 0.3 | 26 | 6 | 0.9 | 24 | 8 | - | 32 | 0 | - |
| 364E/364E (AA) | 6 | 0 | 6 | 0 | 1 | 5 | 5 | 1 | 6 | 0 | 6 | 0 |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

**Table A9:** Concentration ratio of TAM, N-desmethylTAM, 4-OHTAM, and endoxifen, respectively ([NdesMeTAM]/[TAM], [4OHTAM]/[TAM], [Endoxifen]/[NdesMeTAM], and [Endoxifen]/[4OHTAM]), and 17βEstradiol of patients with recurrence and Adverse drug reactions (ADRs) in patients for the study and bivariable logistic regression analysis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | [NdesMeTAM]/[TAM] | [4OHTAM]/[TAM] | [Endoxifen]/[NdesMeTAM] |
|  | < mean  | ≥ mean | p-value | < mean  | ≥ mean | p-value | < mean  | ≥ mean | p-value |
| **Recurrence** |
| No | 17 | 16 | - | 31 | 2 | - | 25 | 8 | - |
| Yes | 1 | 0 | 1 | 0 | 1 | 0 |
| **ADRs** |
| Endometrial cancer |  |  |  |  |  |  |  |  |  |
| No | 19 | 19 | - | 35 | 3 | - | 28 | 10 | - |
| Yes | 0 | 0 | 0 | 0 | 0 | 0 |
| endometrial hyperplasia |  |  |  |  |  |  |  |  |  |
| No | 16 | 19 | - | 32 | 3 | - | 26 | 9 | 0.7 |
| Yes | 3 | 0 | 3 | 0 | 2 | 1 |
| vaginal bleeding |  |  |  |  |  |  |  |  |  |
| No | 18 | 18 | 1 | 33 | 3 | - | 27 | 9 | 0.4 |
| Yes | 1 | 1 | 2 | 0 | 1 | 1 |
| Phlebitis |  |  |  |  |  |  |  |  |  |
| No | 19 | 18 | - | 34 | 3 | - | 27 | 10 | - |
| Yes | 0 | 1 | 1 | 0 | 1 | 0 |
| Headache |  |  |  |  |  |  |  |  |  |
| No | 18 | 18 | 1 | 34 | 2 | 0.09 | 28 | 8 | - |
| Yes | 1 | 1 | 1 | 1 | 0 | 2 |
| Nausea |  |  |  |  |  |  |  |  |  |
| No | 17 | 18 | 0.5 | 32 | 3 | - | 26 | 9 | 0.7 |
| Yes | 2 | 1 | 3 | 0 | 2 | 1 |
| hot flash |  |  |  |  |  |  |  |  |  |
| No | 5 | 7 | 0.4 | 10 | 2 | 0.1 | 7 | 5 | 0.1 |
| Yes | 14 | 12 | 25 | 1 | 21 | 5 |
| Cramps |  |  |  |  |  |  |  |  |  |
| No | 16 | 15 | 0.6 | 29 | 2 | 0.5 | 24 | 7 | 0.2 |
| Yes | 3 | 4 | 6 | 1 | 4 | 3 |
| Bone pain |  |  |  |  |  |  |  |  |  |
| No | 16 | 14 | **0.4** | 28 | 2 | **0.6** | 22 | 8 | 0.9 |
| Yes | 3 | 5 | 7 | 1 | 6 | 2 |
| Urticaria |  |  |  |  |  |  |  |  |  |
| No | 19 | 19 | - | 35 | 3 | - | 28 | 10 | **-** |
| Yes | 0 | 0 | 0 | 0 | 0 | 0 |

*ADR, adverse drug reaction, evaluated with Common Terminology Criteria for Adverse Events [CTCAE], 2010. N.D: No data. ADRs: Endometrial cancer, endometrial hyperplasia, vaginal bleeding, Phlebitis, Headache, Nausea, hot flash, Cramps, Bone pain, and Urticaria. \*Logistic regression*

Continue Table A9

|  |  |
| --- | --- |
| [Endoxifen]/[4OHTAM] | 17βEstradiol |
| < mean  | ≥ mean | p-value | < mean  | ≥ mean | p-value |
|  |  |  |  |  |  |
| 16 | 17 | - | 16 | 4 | - |
| 0 | 1 | 1 | 0 |
|  |
|  |  |  |  |  |  |
| 19 | 19 | - | 18 | 5 | - |
| 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |
| 17 | 18 | 0.5 | 16 | 5 | - |
| 2 | 1 | 2 | 0 |
|  |  |  |  |  |  |
| 18 | 18 | 1 | 16 | 5 | **-** |
| 1 | 1 | 2 | 0 |
|  |  |  |  |  |  |
| 18 | 19 | - | 18 | 4 | - |
| 1 | 0 | 0 | 1 |
|  |  |  |  |  |  |
| 19 | 17 | - | 18 | 4 | - |
| 0 | 2 | 0 | 1 |
|  |  |  |  |  |  |
| 19 | 16 | - | 18 | 4 | - |
| 0 | 3 | 0 | 1 |
|  |  |  |  |  |  |
| 4 | 8 | 0.5 | 7 | 1 | 0.4 |
| 15 | 11 | 11 | 4 |
|  |  |  |  |  |  |
| 15 | 16 | 0.6 | 12 | 5 | - |
| 4 | 3 | 6 | 0 |
|  |  |  |  |  |  |
| 15 | 15 | 1 | 16 | 3 | **0.1** |
| 4 | 4 | 2 | 2 |
|  |  |  |  |  |  |
| 19 | 19 | - | 18 | 5 | - |
| 0 | 0 | 0 | 0 |