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The cytotoxic effects of sertraline on ovarian (A2780) cancer cells *in vitro*

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Abstract

A number of studies have shown that antidepressants can affect cancer cells viability, however, there are few studies focusing on anticancer effects of sertraline on ovarian cancer cells. Therefore, the aim of this study was to investigate the effects of sertraline on cell viability in ovarian (A2780) cancer cells. A2780 cells were divided into control group and groups treated with 1.5625, 3.125, 6.25, 12.5, 25, 50 and 100 µg/ml of sertraline. 24 and 48 hours after treatment, cell viability was assessed by MTT assay method. Data were analyzed using one-way analysis of variance. Treatment with 6.25, 12.5, 25, 50 and 100 µg/ml of sertraline led to significant decrease in cell viability compared to control group 24 and 48 hours after treatment. Although treatment of A2780 cells with 3.125 µg/ml of sertraline did not significantly change the cell viability 24h after treatment, however, treatment of A2780 cells with 3.125 µg/ml of sertraline for 48h significantly decreased the cell viability compared to control group. IC50 value was 11.6 and 5.8 µg/ml for sertraline 24 and 48 hours after treatment, respectively, showing a significant decrease in IC50 (48h) compared to IC50 (24h). The results of this study revealed that sertraline has cytotoxic effects on ovarian cancer cells *in vitro*. Increased treatment duration led to enhanced cytotoxicity of sertraline on ovarian cancer cells.

Keywords: Sertraline, A2780, Viability

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1 Introduction

The ovarian cancer is the fifth cancer leading cause of death among women in worldwide (Lee et al., 2020). This cancer begins from the uterine tubes and enters to the ovaries. Most ovarian cancers are mucosal ovarian cancers and malignant tumors are composed from superficial ovarian cells. The growth of ovarian cancer consists of four stages. The first stage is limited to one or two ovaries, the second stage is transmission to the uterus or organs of near to uterus, the third stage is of transmission to the lymph nodes or abdomen and the fourth stage is transmission to other organs like lungs or liver. Reasons of this cancer are unclear, but several factors have been identified that increase the chances of developing this cancer. These risk factors include age, obesity, family history and genetic factors. Specific gene mutations (such as BRCA1 and BRCA2 mutations) related to breast cancer also increase the chances of developing ovarian cancer. Two or three pregnancies, breastfeeding and the use of hormonal contraceptives pills reduce the risk of ovarian cancer. Common symptoms of this cancer include bloating or pressure in the abdomen, pain in the abdomen or pelvis, increase in the frequency of urination and anorexia (Reid et al., 2017; Stewart et al., 2019).

Studies show that using the antidepressants drugs such as the sertraline may inhibit the development of ovarian cancer. Sertraline (with commercial name Zoloft) is a selective serotonin reuptake inhibitor (SSRIs) (Christensen et al., 2016). Sertraline is effective on panic disorder, generalized anxiety, social anxiety disorder, obsessive-compulsive disorder as well as cognitive disabilities. It may also have anticancer activity against various types of cancers (Liu et al., 2021). Studies have shown that some sedatives or tranquilizers such as antidepressant drugs can overcome drug resistance and be used as anticancer agents (Angelini et al., 2010; Li et al., 2021). Some antidepressants have been reported to have inhibitory effects on growth and proliferation of cancer cells (Song et al., 2021). Laboratory researches have shown that the use of antidepressants reduces the risk of reproductive system cancers (Sperling et al., 2021; Cosgrove et al., 2011). The use of antidepressants has also significant inhibitory effects on ovarian cancer (Cosgrove et al., 2011). Research has shown that sertraline has antitumor activity and reduces grows tumor (Gil-Ad et al., 2008; Bavadekar et al., 2014; Geeraerts et al., 2021). By contrast, some research has shown that the use of benzodiazepine antidepressants, for more than one to six months, increases the risk of ovarian (Harlow and Cramer, 1995; Harlow et al., 1998) and breast (Cosgrove et al., 2011) cancer.

Ovarian cancer is a common cancer among women worldwide (Lee et al., 2020) leading to serious clinical outcomes in patients (Reid et al., 2017; Stewart et al., 2019). Sertraline is also a common antidepressant widely used in patients with cancer (Sheehan and Kamijima, 2009). Studies have shown that sertraline has anticancer activity against cancer cells (Gil-Ad et al., 2008; Bavadekar et al., 2014; Geeraerts et al., 2021); Nevertheless, conflictive data have been reported regarding the anticancer impact of sertraline on cancer cells (Angelini et al., 2010; Li et al., 2021; Christensen et al., 2016; Harlow and Cramer, 1995; Harlow et al., 1998). Few studies also have been carried out to investigate the anticancer effects of sertraline on ovarian cancer cells *in vitro*. The aim of this study was to determine the cytotoxic effects of sertraline on ovarian (A2780) cancer cells *in vitro*.

2 Materials and Methods

In this experimental-laboratory study, ovarian cancer (A2780) cells were purchased from Iran Cell Bank (Pasteur Institute, Tehran). Sertraline was prepared from a pharmaceutical company (Iran Daroo) as pure powder and was maintained in normal laboratory temperature of 25°C. To prepare different concentrations of sertraline, 100 µl of sodium hydroxide solution was added to 1 gram of sertraline powder. To increase the solubility, 1000 µl of phosphate buffer solution (PBS) was added to the solution. The resulting solution was sterilized and filtered by syringe filter. 9 mL of DMEM culture medium containing fetal bovine serum was added to the prepared solution to reach a volume of 10 ml and the desired concentrations were prepared from this solution.

Ovarian cancer cells were divided into control group and groups treated with 1.56, 3.12, 6.25, 12.5, 25, 50 and 100 µg/mL of sertraline. A2780 cells were defreezed and transferred to cell culture flasks containing DMEM culture medium, bovine fetal serum (Sigma) and FBS. After reaching 80% confluency, 10^5 cells were added to each well of microplates and the culture medium was added. Then microplates were incubated at 37 °C, appropriate humidity and 5% carbon dioxide for 24 hours. MTT assay was used to measure the cytotoxic effects of sertraline on cancer cells (Ahmadi et al., 2017; Norouzi et al., 2020). Different doses of sertraline were added to a row of wells containing cell cultivated and repeated 3 times for each concentration. Also, a row of wells was maintained and considered as a control group (without treeatment). Then plates were incubated for 24 hours (37 °C and 5% carbon dioxide). After 24 hours, the liquid on the wells (containing the culture medium and sertraline) was removed. In the next step, MTT dye was prepared according to the sigma company protocol and 100 µl of DDT 10% was added to each well. After 4-6 hours, the solution was removed and 200 µl DMSO (Sigma Company) was added to each well resulting in formation of insoluble purple formazan crystals. Finally, light absorption was read using ELISA reader (Bio-Rad, Hercules, CA, USA) at 570 nm and the cell viability percentage was calculated using the following formula:

$$\%\text{Viability} = \text{Mean OD sample} / \text{Mean OD blank} \times 100$$

Sertraline IC50 (half-maximal inhibitory concentration) was calculated by linear approximation regression of the percentage viability versus the sertraline concentration.

The data were analyzed using SPSS21 software (IBM company, USA) by one-way analysis of variance followed by Tukey's post hoc test. P-value ≤0.05 was statically significant.

3 Results and Discussions

Treatment of A2780 cells with sertraline 6.25, 12.5, 25, 50 and 100 µg/ml of sertraline led to significant decrease in cell viability 24 and 48 hours after treatment compared to control group. Although treatment of A2780 cells with 3.125 µg/ml of sertraline for 48 hours significantly decreased the cell viability, percentage of cell viability did not significantly change in A2780 cells treated with 3.125 µg/ml of sertraline for 24 hours compared with control group. The

lowest concentration of sertraline (1.5612 µg/ml) did not have significant impact on A2780 cells viability 24h and 48h after treatment compared with control group (Figure 1 and 2).

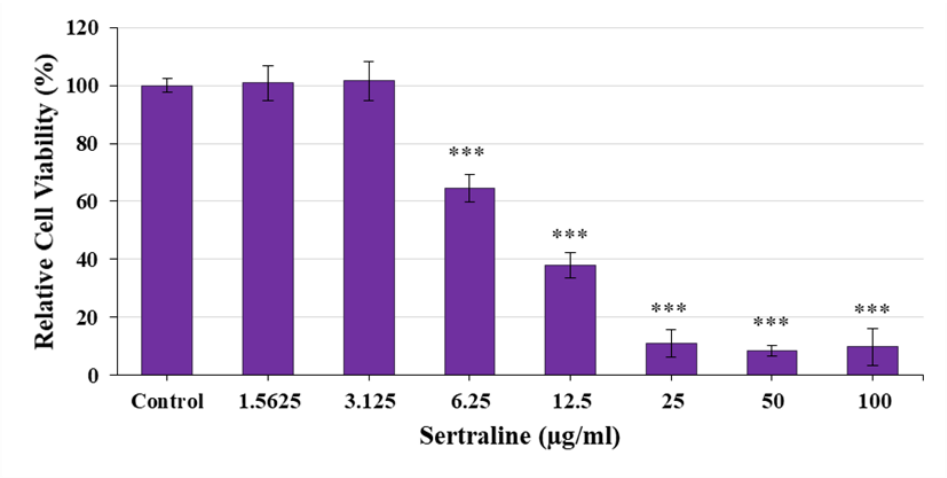

Figure 1. Viability of A2780 cells treated with different concentrations of sertraline 24 hours after treatment. * indicates significant difference compared with control group (***:P<0.001).

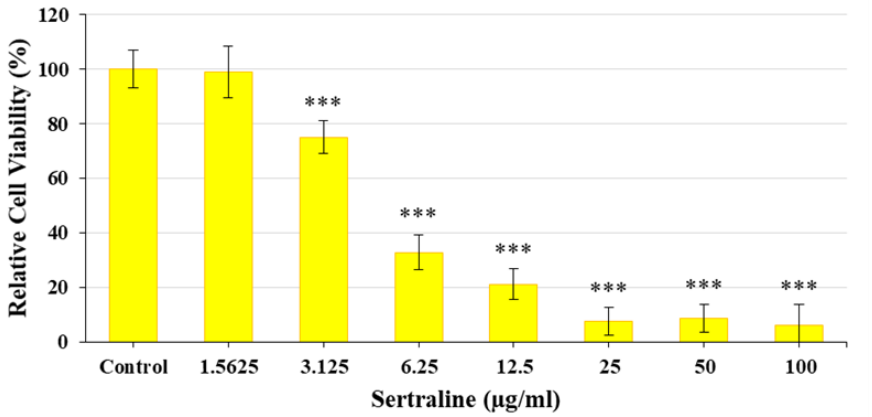

Figure 2. Viability of A2780 cells treated with different concentrations of amitriptyline 48 hours after treatment. * indicates significant difference compared with control group (***:P<0.001).

The results showed that the IC50 value was 11.6 and 5.8 µg/ml for sertraline 24 and 48 hours after treatment, respectively, showing a significant decrease in IC50 (48h) compared to IC50 (24h) (Figure 3 and 4).

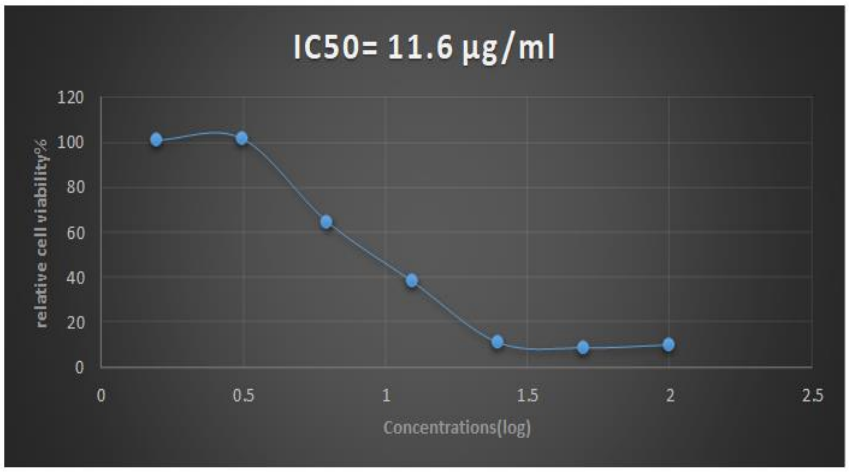

Figure 3. IC50 of sertraline calculated from curve constructed by plotting A2780 cell viability (%) versus sertraline 24 hours after treatment.

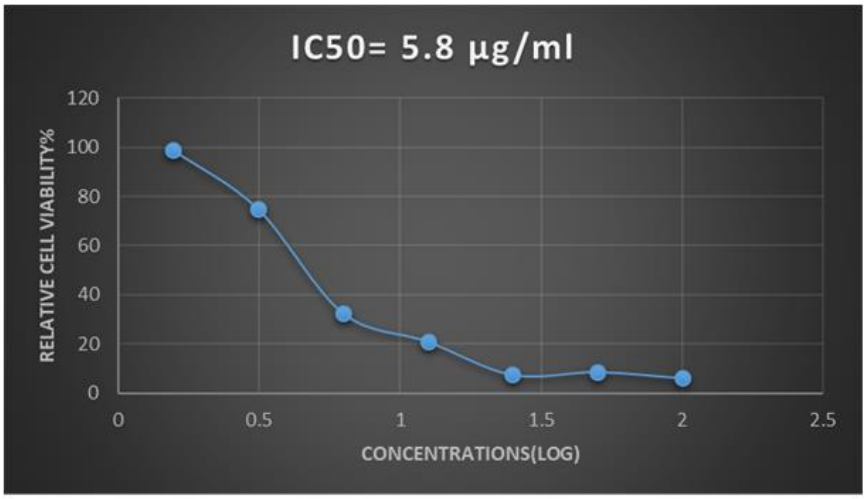

Figure 4. IC50 of sertraline calculated from curve constructed by plotting A2780 cell viability (%) versus sertraline 48 hours after treatment.

Many studies have shown that sertraline play key role in the treatment of cancer. The results of this study show that sertraline can reduce cell viability of ovarian cancer *in vitro*. In line with our findings, sertraline has been reported to have cytotoxic effects on cancer cells (Mørch et al., 2017). Anticancer activity of sertraline has been reported against breast cancer cells (Budajaja, 2014). The results of a study on the association of antidepressants with cancer show that many antidepressants including sertraline have important inhibitory effect on cancer progression and tumor growth (Liu et al., 2020; Toh et al., 2007; Lee et al., 2021; Chan et al., 2018; Di Rosso et al., 2018). By contrast, it has been reported that long term use of antidepressants may increase the risk of ovarian cancer (Harlow et al., 1998; Coogan et al., 2000).

The possible inhibitory mechanism of sertraline action on A2780 ovarian cancer cell line is, at least in part, mediated by sertraline inhibitory effects on mitochondrial function (Geeraerts et al., 2021). Sertraline is also able to inhibit Translational Controlled Tumour Proteins (TCTPs), by

which may exert its cytotoxic effects on cancer cells (Baú-Carneiro et al., 2022). However, further research are required to reveal the exact molecular mechanism behind the sertraline action on ovarian cancer cells.

4 Conclusion

We have shown that sertraline has cytotoxic impact on ovarian A2780 cancer cells *in vitro*. Increased treatment duration enhances the cytotoxic effects of sertraline on ovarian cancer cells.

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References

Ahmadi, R., Sagharjoghi Farahani, M., & Azadkhah, R. (2017). The Effects of Diclofenac and Ibuprofen on HEK Cells in Cell Culture. *Yafte*, *19*(4). http://eprints.lums.ac.ir/id/eprint/1069

Angelini, A., Di Ilio, C., Castellani, M. L., Conti, P., & Cuccurullo, F. (2010). Modulation of multidrug resistance p-glycoprotein activity by flavonoids and honokiol in human doxorubicin-resistant sarcoma cells (MES-SA/DX-5): implications for natural sedatives as chemosensitizing agents in cancer therapy. *Journal of Biological Regulators and Homeostatic Agents*, *24*(2), 197-205. PMID: 20487633

Baú-Carneiro, J. L., Sumida, I. A. G., Gallon, M., Zaleski, T., Boia-Ferreira, M., & Cavassin, F. B. (2022). Sertraline repositioning: an overview of its potential use as a chemotherapeutic agent after four decades of tumor reversal studies. *Translational Oncology*, *16*, 101303. https://doi.org/10.1016/j.tranon.2021.101303

Bavadekar, S., Panchal, P., Hanbashi, A., & Vansal, S. (2014). Cytotoxic effects of selective serotonin-and serotonin-norepinephrine reuptake inhibitors on human metastatic breast cancer cell line, MCF-7 (842.3). *The FASEB Journal*, *28*, 842-3. https://doi.org/10.1096/fasebj.28.1_supplement.842.3

Budajaja, F. (2014). *Anti-Proliferative Mechanism of Selective Serotonin Re-uptake Inhibitor–Sertraline-on Human Metastatic Breast Cancer Cell Line, MDA-MB-231* (Doctoral dissertation, Long Island University, The Brooklyn Center).

Chan, H. L., Chiu, W. C., Chen, V. C., Huang, K. Y., Wang, T. N., Lee, Y., McIntyre, R. S., Hsu, T. C., Lee, C. T., & Tzang, B. S. (2018). SSRIs associated with decreased risk of hepatocellular carcinoma: A population-based case-control study. *Psycho-Oncology*, *27*(1), 187-192. https://doi.org/10.1002/pon.4493

Christensen, D. K., Armaiz-Pena, G. N., Ramirez, E., Matsuo, K., Zimmerman, B., Zand, B., Shinn, E., Goodheart, M. J., Bender, D., Thaker, P. H., Ahmed, A., Penedo, F. J., DeGeest, K., Mendez, L., Domann, F., Sood, A. K., & Lutgendorf, S. K. (2016). SSRI use and clinical outcomes in epithelial ovarian cancer. *Oncotarget*, *7*(22), 33179-33191. https://doi.org/10.18632/oncotarget.8891

Coogan, P. F., Rosenberg, L., Palmer, J. R., Strom, B. L., Stolley, P. D., Zauber, A. G., & Shapiro, S. (2000). Risk of ovarian cancer according to use of antidepressants, phenothiazines, and benzodiazepines (United States). *Cancer Causes & Control*, *11*(9), 839-845. https://doi.org/10.1023/a:1008982417022

Cosgrove, L., Shi, L., Creasey, D. E., Anaya-McKivergan, M., Myers, J. A., & Huybrechts, K. F. (2011). Antidepressants and breast and ovarian cancer risk: a review of the literature and researchers' financial associations with industry. *PLoS One*, *6*(4), e18210. https://doi.org/10.1371/journal.pone.0018210

Di Rosso, M. E., Sterle, H. A., Cremaschi, G. A., & Genaro, A. M. (2018). Beneficial effect of fluoxetine and sertraline on chronic stress-induced tumor growth and cell dissemination in a mouse model of lymphoma: crucial role of antitumor immunity. *Frontiers in Immunology*, *9*, 1341. https://doi.org/10.3389/fimmu.2018.01341

Geeraerts, S. L., Kampen, K. R., Rinaldi, G., Gupta, P., Planque, M., Louros, N., Heylen, E., De Cremer, K., De Brucker, K., Vereecke, S., Verbelen, B., Vermeersch, P., Schymkowitz, J., Rousseau, F., Cassiman, D., Fendt, S. M., Voet, A., Cammue, B., Thevissen, K., & De Keersmaecker, K. (2021). Repurposing the Antidepressant Sertraline as SHMT Inhibitor to Suppress Serine/Glycine Synthesis–Addicted Breast Tumor Growth. *Molecular Cancer Therapeutics*, *20*(1), 50-63. https://doi.org/10.1158/1535-7163.mct-20-0480

Gil-Ad, I., Zolokov, A., Lomnitski, L., Taler, M., Bar, M., Luria, D., Ram, E., & Weizman, A. (2008). Evaluation of the potential anti-cancer activity of the antidepressant sertraline in human colon cancer cell lines and in colorectal cancer-xenografted mice. *International Journal of Oncology*, *33*(2), 277-286. https://doi.org/10.3892/ijo_00000007

Harlow, B. L., & Cramer, D. W. (1995). Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: evidence from two combined case-control studies (Massachusetts, United States). *Cancer Causes & Control*, *6*(2), 130-134. https://doi.org/10.1007/bf00052773

Harlow, B. L., Cramer, D. W., Baron, J. A., Titus-Ernstoff, L., & Greenberg, E. R. (1998). Psychotropic medication use and risk of epithelial ovarian cancer. *Cancer Epidemiology and Prevention Biomarkers*, *7*(8), 697-702. PMID: 9718222

Lee, J. Y., Yang, C., Lim, W., & Song, G. (2020). Methiothepin suppresses human ovarian cancer cell growth by repressing mitochondrion-mediated metabolism and inhibiting angiogenesis in vivo. *Pharmaceutics, 12*(7), 686. https://doi.org/10.3390/pharmaceutics12070686

Lee, M. J., Huang, C. W., Chen, Y. L., Yang, Y. H., & Chen, V. C. H. (2021). Association between

selective serotonin reuptake inhibitors and kidney cancer risk: A nationwide population-based cohort study. *International Journal of Cancer*, *148*(6), 1331-1337. https://doi.org/10.1002/ijc.33307

Li, T., Yang, J., Yang, B., Zhao, G., Lin, H., Liu, Q., Wang, L., Wan, Y., & Jiang, H. (2021). Ketamine Inhibits Ovarian Cancer Cell Growth by Regulating the lncRNA-PVT1/EZH2/p57 Axis. *Frontiers in Genetics*, 1486. https://doi.org/10.3389/fgene.2020.597467

Liu, W., Li, G., Wang, C., Wang, X., & Yang, L. (2021). Efficacy of Sertraline Combined with Cognitive Behavioral Therapy for Adolescent Depression: A Systematic Review and Meta-Analysis. *Computational and Mathematical Methods in Medicine*, *2021*. https://doi.org/10.1155/2021/5309588

Liu, Y. C., Chen, V. C., Lu, M. L., Lee, M. J., McIntyre, R. S., Majeed, A., Lee, Y., & Chen, Y. L. (2020). The association between selective serotonin reuptake inhibitors (SSRIs) use and the risk of bladder cancer: a nationwide population-based cohort study. *Cancers*, *12*(5), 1184. https://doi.org/10.3390/cancers12051184

Mørch, L. S., Dehlendorff, C., Baandrup, L., Friis, S., & Kjær, S. K. (2017). Use of antidepressants and risk of epithelial ovarian cancer. *International Journal of Cancer*, *141*(11), 2197-2203. https://doi.org/10.1002/ijc.30919

Norouzi, S., Ahmadi, R., & Pashapour, S. (2020). The cytotoxic effects of Tolmetin on evaluation of Bax and Bcl2 genes expression level in cervical cancer cells (Hela). *KAUMS Journal (FEYZ)*, *24*(1), 31-37. http://feyz.kaums.ac.ir/article-1-3950-en.html

Reid, B. M., Permuth, J. B., & Sellers, T. A. (2017). Epidemiology of ovarian cancer: a review. *Cancer Biology & Medicine*, *14*(1), 9–32. https://doi.org/10.20892/j.issn.2095-3941.2016.0084

Sheehan, D. V., & Kamijima, K. (2009). An evidence-based review of the clinical use of sertraline in mood and anxiety disorders. *International Clinical Psychopharmacology*, *24*(2), 43-60. https://doi.org/10.1097/yic.0b013e3282f4b616

Song, Y., Yang, X., & Yu, B. (2021). Repurposing antidepressants for anticancer drug discovery. *Drug Discovery Today*. https://doi.org/10.1016/j.drudis.2021.10.019

Sperling, C. D., Aalborg, G. L., Dehlendorff, C., Friis, S., Mørch, L. S., & Kjaer, S. K. (2021). Use of antidepressants and endometrial-cancer risk: a nationwide nested case–control study. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyab200

Stewart, C., Ralyea, C., & Lockwood, S. (2019, April). Ovarian cancer: an integrated review. In *Seminars in Oncology Nursing* (Vol. 35, No. 2, pp. 151-156). WB Saunders. https://doi.org/10.1016/j.soncn.2019.02.001

Toh, S., Rodríguez, L. A. G., & Hernández-Díaz, S. (2007). Use of antidepressants and risk of lung cancer. *Cancer Causes & Control*, *18*(10), 1055-1064. https://doi.org/10.1007/s10552-007-9045-1