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The use of tamoxifen in the treatment and prevention of breast cancer

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Abstract:

Breast cancer is the most frequently occurring malignant neoplasm among women. Statistically, it constitutes 22,8% of all malignant neoplasms among females. Despite the fact that the causes of the disease remain unknown, a few risk factors are contributing to its development.

Age, family history, type of lifestyle, hormones and genetic background have a significant association with occurrence of breast cancer. Due to the fact that time in which female sex hormones affect mammary gland is one of the most important risk factors of breast cancer development, more researchers focused on the use of drugs such as selective estrogen receptor modulators (SERMs) in the disease prevention. Tamoxifen has antiestrogenic effect. That results in the inhibition of both- growth factors release and synthesis by the tumour. Moreover, this drug works as agonist, replacing oestrogen to many tissues, such as the ones in liver, bone, breast and uterus. In the literature there are many reports about the effectiveness of tamoxifen in the prevention of breast cancer. The drug, in addition to using it as adjuvant therapy for breast

cancer, can be used as a prophylactic of the disease. Side effects of the drug are rare, but they cannot be completely excluded.

Breast cancer, which is currently the most common tumour in the globe, is a serious worldwide public health quandary. Tamoxifen is considered to be a pioneering drug as it is used in combined breast cancer therapy and also in chemoprophylaxis ,but every case of using the medicine should be considered individually to assess benefit-risk ratio.

Key words: tamoxifen, breast cancer, selective estrogen receptor modulators, prevention

Introduction

Breast cancer is the most frequently occurring malignant neoplasm among women. Statistically, it constitutes 22,8% of all malignant neoplasms among females. It is the second most common cause of the death of women due to the cancer. It is also the most frequently occurring type of neoplasm in developed countries (USA, Western Europe), whereas in South Asia and Africa its incidence is much lower.[1] The 5-year survival rate of patients diagnosed in Poland in 2008-2010 is 79%. The National Cancer Registry states that at the time of diagnosis in 2016, 66% of cases were local, 26% regional and about 7% generalized. Referring to data from 2010 (local advancement - 58% of cases, regional 26%, generalized 8%), an increase in the frequency of breast cancer detection at a less advanced stage was observed, however, still a large proportion of patients report to the doctor only when the disease is at serious stage of advancement.[2] The risk increases with age to the seventh decade of life, but afterwards we can observe a decrease in its prevalence. In comparison to other European Union countries in Poland the average incidence of breast cancer is 35% lower, while mortality is 20% lower than in other countries. [3] The peak of breast cancer incidence is 55-69 years. Currently, we can observe an increase in the occurrence of breast cancer, while from the mid-90s of the last century, the mortality decreased [2,3].

Despite the fact that the causes of the disease remain unknown, risk factors contributing to its development have been identified. The risk of becoming ill increases with age, which is considered as the most significant factor among all. The incidence of breast cancer in women before the age of 35 is estimated to be about 1-3% and most often concerns cases of aggressive biology as well as cases on the hereditary basis. The majority of cases concern women after their 50s. Women in the age of 50-59 are 32% of all patients. [4,5,6] The incidence of breast

cancer in the family is also an important risk factor, especially in first degree relatives. Such relationship can be observed even in 25% of patients.[4] The likelihood of developing this cancer increases with the number of first-degree relatives who have been affected.[1] Other particularly important risk factors include the presence of breast cancer in anamnesis, atypical hyperplasia, high-density breasts, and exposure to ionizing radiation.[4] Type of lifestyle also has a significant impact on the development of the disease. Research indicates relationship between increased percentage of illness and the intake of large amounts of fats in the diet, obesity, smoking and alcohol consumption [1].

The risk of developing breast cancer is also increased by the early age of menarche and the menopause in late life, which is related to the prolongation of exposure time of the sensitive mammary gland to the hormones produced by the ovary - estrogen and progesterone.[1] Also the age at which the woman gave birth to the first child is significant. Women who have been pregnant for the first time after their 30s have two times higher risk of cancer development than women who gave birth for the first time in their 20s. Long-term exposure to estrogens is a documented risk factor which has led researchers to study the effects of hormone replacement therapy (HRT) and hormonal contraception on the incidence of breast cancer. There was observed an increased risk of developing this tumor in women using HRT, while exposure lasting less than 5 years was not associated with a significant increase in cancer development. [4,7] Moreover according to American scientists the risk of using HTR less than five years is smaller than the risk related to obesity and alcohol consumption. What is crucial among patients using HTR there have been observed more often mammography examination, which influences on cancer's detection rate. [4,8] The majority of studies concerning oral hormonal contraception (HTA) did not show a significant increase in the incidence of women taking it, but there was identified a group of patients in whom this therapy may increase the risk up to 70%. It includes patients who do not become pregnant [7,9]. The period of use of HTA up to 2 years has been considered safe, while patients taking HRT beyond 8 years are said to be exposed to an increased risk of disease by up to 46% [4].

Genetic background of breast cancer is found in approximately 5-10% of cases. The most significant risk factor for the development of hereditary cancer is an emergence of mutations in suppressor genes BRCA1 and BRCA2. These genes show biological activity including repair of damaged DNA. On the other hand, an occurrence of mutations is responsible for development of genetically conditioned co-existing breast and ovarian cancer [10]. That may lead to emergence of either breast cancer, ovarian cancer or these two tumors simultaneously among women within one family. Additionally, a characteristic trait is young age of tumor

development and its aggressive course. Ovarian cancer associated with BRCA1 and BRCA2 mutations has specific phenotype - the most common is serous and endometroid cancer [11,12,13]. Moreover, these genes are probably related to primary Fallopian tube cancer and peritoneal cancer [14]. The occurrence of this mutation increases the risk of both- breast cancer to 80% and ovarian cancer to 30%. References indicate that among the carriers of BRCA1 gene, the incidence of breast cancer is estimated around 65% among 70-year-old women. Regarding women with BRCA2 mutation, the value is lower and concern approximately 45% of cases [10]. An individual risk index of patients with mutations is difficult to estimate as around 2000 variants of mutations have been found in these genes. The studies indicated that the place where mutant variant is located, may have a greater risk of developing breast cancer [10,15,16]. Moreover, recent researches suggest that the risk factors of breast cancer may influence carriers of BRCA1 and BRCA2 in different way than women that do not have mutation [17]. Additionally, other genes may induce the development of the illness- ATP, BRIP1, TP3, CHEK i PTEN [1].

Tamoxifen

Due to the fact that time in which female sex hormones affect mammary gland is one of the most important risk factor of breast cancer development, more researchers focused on the use of drugs such as selective estrogen receptor modulators (SERMs) in prevention breast cancer. Distinctive interest concerns the application of tamoxifen that has been used as an element of combined oncological treatment. The use of tamoxifen in breast cancer prophylaxis could be a breakthrough in oncology and reduce the number of new cases in significant rate [18].

Tamoxifen has antiestrogenic effect. It combines competitively with estrogen's receptors in tissues of the cancer that express them. That results in the inhibition of both- growth factors release and synthesis by the tumour [18]. Moreover This drug works as agonist, replacing oestrogen to many tissues, such as the ones in liver, bone, breast and uterus. [2]Additionally, tamoxifen stimulates the development of progesterone receptors. Its action leads to inhibition of tumour cells division in breast. Moreover, it increases the concentration of sex hormone binding globulin that results in the decrease of free estradiol level in a plasma. That causes the stimulation of anterior pituitary gland that results in FSH secretion which stimulates the ovaries to secrete estrogens in premenopausal period. What is more, tamoxifen has an impact on the release of transforming growth factor β (TGF-β) that contributes to its antineoplastic activity [18].

Tamoxifen is well absorbed from the digestive tract and reaches maximum concentration around 4-7 hours after oral administration. The half-life is 7-14 days. It binds to 99% of plasma proteins. The main metabolite of tamoxifen is demethylamamoxifen that has similar activity. The drug is excreted mainly in form of metabolites along with faeces [18].

Tamoxifen is a first-line drug for a women with positive oestrogen receptor breast cancer. According to researches, it does not work for oestrogen receptor negative breast cancer. [19]. This drug works as agonist, replacing oestrogen to many tissues, such as the ones in liver, bone, breast and uterus [20]. It is estimated, that this therapy decreases the currency of a breast cancer for about 50% [21,22]. Among women in pre menopause period, tamoxifen can be an alternative to oophorectomy or ovarian irradiation. As reported by many researchers, we can also use it as an induction of an ovulation, and in therapy of mastalgia and mastopaty. This kind of therapy has also utilisation in decreasing the risk of a breast cancer among women with carcinoma in situ after the operation and radiotherapy, or belonging to high-risk group [18].

Side effects

Side effects of tamoxifen therapy are rare, but it is recommended to just lower the dose of the drug to reduce the symptoms. Women treated with tamoxifen, had higher risk of endometrial cancer, especially those over the age of 50. Moreover, they were more prone to have deep venous thrombosis and pulmonary embolism. [23] One of the Italian randomised study, indicates that patients taking tamoxifen, were more likely to have hot flashes and urinary disturbances. The same research suggested that women with this therapy had more thromboembolic events, cardiac arrhythmia, atrial fibrillation and higher risk of hypertriglyceridemia [24] However, some of the results revealed, that tamoxifen therapy when stopped, discontinued to cause deep vein thrombosis and pulmonary embolism. [25,26] It is also common to have vasomotor symptoms, because of the lack of oestrogenes, such as redness of a face, rash, nausea, vomiting, dizziness and headaches, menstrual disorders or bone pain [18].

The use of tamoxifen as a breast cancer prophylaxis

In the literature there are more and more frequent reports about the effectiveness of tamoxifen in the prevention of breast cancer. Tamoxifen is considered to be a pioneering drug as it is use in combined breast cancer therapy and also in chemoprophylaxis. Anti-estrogen therapy can be usage in the types of cancers associated with hormones as well as for tumors showing estrogen receptor expression [27]. Due to the fact that the drug has both estrogenic and antiestrogenic

activity, it seems that it's use can bring significant benefits, but it also has side effects. Most of the studies focuses on understanding the benefit / risk ratio and tries to define groups, which probably could take advantage of. In many randomized trials, the effectiveness of the drug in reducing the risk of cancer development has been proven [28] Food and Drug Administration (FDA) considered the medicine as a chemoprophylaxis in 1998. They classified women in the pre- and postmenopausal period with ,increased hereditary risk of breast cancer [29,30]. The decision was based on the result of study which was carried out by the United States National Cancer Institute. The research was ended earlier because as an intervening study showed that tamoxifen lowered breast cancer prevalence by almost one half [22,29].

A few prospective randomized trials have been conducted to test the effectiveness of the drug in prevention of breast cancer [31]. One of one of the aforementioned tests was conducted by The National Surgical Adjuvant Breast and Bowel Project P-1 study (NSABP-P1) in 1992. They qualified randomized 13,388 women with a 5-year predicted breast cancer risk of at least 1.66% by the modified Gail model. After a follow-up of 54.6 months on average, a 49% decrease in risk was seen in the tamoxifen group. It was proved that tamoxifen had reduced risk in all age groups in patients with a history of lobular carcinoma in situ (LCIS) or atypical ductal hyperplasia. It was also considered to be effective with women, who had high classification of predicted 5-year risk. However there was no significant change in risk in ER-negative tumors [29].

The Italian Randomized Tamoxifen Prevention Trial, which enrolled 5408 participants, initially did not show the efficacy of tamoxifen in reducing risk. The study involved also women with low-to-normal risk of breast cancer. Notwithstanding, after 11 years of observation scientist verified a statistically significant reduction in the prevalence of ER-positive breast cancer among patients with high risk who received the drug [32,33].

The Royal Marsden Hospital Tamoxifen Chemoprevention Trial failed to demonstrate effectiveness of the medicine in the beginning. It randomized 2494 women who were 30-70 years old and had a family history of breast cancer. In 2007 the up-date of this trial was published and it showed that tamoxifen had reduced a risk of the ER-positive cancer based on the conclusions from 20 years of observation [34,35].

In the years 1992-2001 The International Breast cancer Intervention Study I (IBIS-I) was conducting a research, to which women were qualified who had a family history of breast cancer. Participants were devoted into 2 groups. One of these groups received the drug at 20 mg daily for 5 years , while the second group received a placebo for the same time. 7154 women, who were examined have been observed on average for 16 years. The results of this

research were promising. It was found that group who had received tamoxifen had significantly lower risk of developing breast cancer compared to those receiving placebo. Risk decrease was remarkably visible in the case of invasive oestrogen receptor-positive breast cancer. There was also a lower risk of developing ductal carcinoma in situ (DCIS), but only in the first 10 years of observation. What it is more, the study showed lower risk of gastrointestinal cancer. However there was no significant difference in the incidence of invasive oestrogen receptor-negative breast cancer. What is important, no statistically significant difference in the incidence of cerebral, vascular or death was found, however, the incidence of deep vein thrombosis was more frequent in the tamoxifen group. The published study proves that tamoxifen is effective in reducing the risk of breast cancer [36,37].

Tamoxifen gives long-term defence and is the only proven preventive therapy for premenopausal women. What is more, the lasting long-standing effect is not only seen during treatment, but it also persists in the 5 years after therapy was completed. Furthermore after the end of tamoxifen therapy almost all side-effects cease [38]. In recent years, the National Institute for Health and Care Excellence in the United Kingdom has published guidelines, which recommend using the drug for 5 years for women with a 30% lifetime risk of breast cancer and probably with women who have a 19% lifetime risk and do not have increased risk of thromboembolic diseases [39]. It is established that tamoxifen reduce the risk of contra-lateral breast cancer and it is even more effective than contra lateral prophylactic mastectomy [40].

It is also recognized that tamoxifen prevents the development of breast cancer to the same extent as prophylactic adneksectomy in women with the highest genetic risk of breast cancer [41,42,43]. Data on the effectiveness of the drug in primary prevention in patients with inherited mutations come mainly from trials conducted by Royal Marsden [44] and NSABP-P1 [45]. Trials which enrolled 2464 mutation carriers presented that the medicine lowered the risk of development of contra-lateral breast cancer in women who had suffered from the disease [46,47]. Majority of breast cancer with BRCA1 mutation is ER-negative, while tamoxifen is considered to be the most effective with cancer what express estrogen receptors. This prompted researchers to study the effectiveness of the drug in BRCA1 carcinomas. Collected data suggested that the medicine can decrease hormone receptor negative tumors in BRCA1 mutation carriers as well [47]. It also indicated that estrogen plays a huge role in the beginning of oncogenesis processes of tumors with BRCA1 mutations [48]. Tamoxifen has no impact on decreasing the risk of development ovarian cancer in women with BRCA1 and BRCA2 mutations, however increases the risk of endometrium cancer several times [29,41,49]. The three years of application of the drug protects patients with these mutations against breast cancer

for a period of 10 years. Such prevention is recommended for patients from 35 to 40 years old, but it is not widely used. In the United States group, which could have some benefits from this therapy is significantly limited [30]. Tamoxifen should be considered with patients with BRCA1 and BRCA2 mutations who refuse bilateral mastectomy or want to significantly delay it. Especially in the case of for premenopausal women this therapy can bring meaningful benefits and risk of important side effects is potentially small. For mutation carriers who have been identified with hormone receptor positive tumors, the medicine is believed to be a standard of care [48,50].

The main limitation in the use of tamoxifen by patients from high-risk groups and their doctors is the fear of side effects. One of proposed strategies to improve benefit-risk ratio was to use the drug at low doses to minimize the risk of undesirable consequences of therapy. Carried out researches reports that low-dose tamoxifen therapy can reduce toxicity of the drug, while the biological activity is retained. [48]. The conventional dose used for prophylaxis is 20 mg/day. It was found that efficacy of 20 mg/day of tamoxifen is comparable to that of upper doses of the drug (30-40 mg/day) [51]. Interestingly, data from animal studies suggested that reducing the dose of the drug up to 1 mg does not involve a significant reduction in the effectiveness of the drug [52]. On the other hand, the minimum active dose of the drug has not been determined so far. In order to investigate whether the reduction of the standard dose in prophylaxis reduces the activity of the drug, several studies have been carried out. They assessed the effect of different doses of the drug on different biomarkers such as IGF-1 and Ki-67, which were known to be favourably touched by conventional tamoxifen dose [48]. In 1992 Decensi et al. were investigating associations between various doses of the drug and biomarkers. They didn't manage to observe a significant change in levels of biomarkers, which was caused by different tamoxifen dose. The only response was seen for the ratio of IGF-1/IGF binding proteins (IGFBP)-3 [53]. In 2003 they found that effect on Ki-67 expression of the lower dose of the medicine is comparable to the higher dose [54]. The other studies also showed that minor dose of the drug had no impact on the activity in prophylaxis [55].

Conclusions

Breast cancer, which is currently the most common tumour in the globe, is a serious worldwide public health quandary. The use of tamoxifen seems to be a breakthrough in its treatment and prevention. The drug, in addition to using it as adjuvant therapy for breast cancer, can be used as a prophylactic of the disease. Tamoxifen can stop the development of the disease and reduce the risk of its occurrence in women at high risk. In a few randomized trials on large groups

researches demonstrated effectiveness of the medicine and benefits of therapy. The results substantially improve benefit-risk ratio, but every case of using tamoxifen should be considered individually to assess it. Serious side effects such as thromboembolic complications, endometrium cancer or thrombocytopenia are rarely reported. Redness of the face, flushing, rash, nausea, vomiting, dizziness and headaches are the most common aftereffects. Younger women are less affected by the adverse effects of therapy. Tamoxifen can bring visible advantages especially to premenopausal women, who are more tolerant of treatment. The drug is particularly beneficial for patients with a family history of breast cancer and carriers of the BRCA1 and BRCA2 mutation. The main limitation of its use is the fear of side effects. Both patients and physicians should be educated about the benefits of this therapy. Tamoxifen prophylaxis is generally available and low cost. Its global introduction can significantly reduce the number of new cases and protect the patient against aggravating treatment.

Bibliography:

1. http://onkologia.org.pl/rak-piersi-kobiet/
2. Urszula Wojciechowska, Krzysztof Czaderny, Agata Ciuba, Paweł Olasek, Joanna Didkowska; Nowotwory złośliwe w Polsce w 2016r.
3. http://onkologia.org.pl/nowotwory-piersi-kobiet/
4. Redakcja naukowa prof. dr hab. n. med. Jan Kornafel, Marcin Ekiert, Iwona Gisterek, Agnieszka Ignatowicz-Pacyna, Michał Jeleń, Aleksandra Łacko, Rafał Matkowski, Ewa Nienartowicz, Katarzyna Soter, Krzysztof Szewczyk, Radosław Tarkowski, Marek Woźniewski; Rak piersi; Warszawa 2011
5. Pieńkowski T: Rak piersi. W: onkologia kliniczna. red. Krzakowski M, Borgis Wydawnictwo Medyczne, Warszawa, pp87-140, 2001.
6. Greenlee RT, Murray T, Bolden S and Wingo PA: Cancer statistics, 2000. CA Cancer J Clin 50: 7-33, 2000.
7. Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 350: 1047-1059, 1997.
8. Speroff L: i wsp.: The effect of oestrogen – progestogen postmenopausal hormone replacement therapy on the cardiovascular system. Eur. Menopause J. 3: 151-163, 1996.
9. Romieu I, Berlin JA and Colditz G: Oral contraceptives and breast cancer. Review and meta-analysis. Cancer 66: 2253-2263, 1990.
10. Awareness and current knowledge of breast cancer, Muhammad Akram, Mehwish Iqbal, Muhammad Daniyal and Asmat Ullah Khan; Akram et al. Biol Res (2017) 50:33
11. Boyd J, Sonoda Y, Federici MG, Bogomolniy F, Rhei E, Maresco DL, et al. Clinicopathologic features of BRCAlinked and sporadic ovarian cancer. JAMA 2000;283: 2260–5. (Level II-3)
12. Lakhani SR, Manek S, Penault -Llorca F, Flanagan A, Arno -ut L, Merrett S, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. Clin Cancer Res 2004;10:2473–81. (Le vel II -3)
13. Berchuck A, Heron KA, Carney ME, Lancaster JM, Fraser EG, Vinson VL, Deffenbaugh AM, Miron A, Marks JR, Futreal PA, et al: Frequency of germline and somatic BRCA1 mutations in ovarian cancer. Clin Cancer Res 4: 2433-2437, 1998. (Level III).

14. Levine DA, Argenta PA, Yee CJ, Marshall DS, Olvera N, Bogomolniy F, Rahaman JA, Robson ME, Offit K, Barakat RR, et al: Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. J Clin Oncol 21: 4222-4227, 2003. (Level III).

15. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, Loman N, Olsson H, Johannsson O, Borg A, et al: Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: A combined analysis of 22 studies. Am J Hum Genet 72: 1117-1130, 2003.

16. Scott CL, Jenkins MA, Southey MC, Davis TA, Leary JA, Easton DF, Phillips KA and Hopper JL: Average age-specific cumulative risk of breast cancer according to type and site of germline mutations in BRCA1 and BRCA2 estimated from multiple-case breast cancer families attending Australian family cancer clinics. Hum Genet 112: 542-551, 2003.

17. Nkondjock A and Ghadirian P: Epidemiology of breast cancer among BRCA mutation carriers: An overview. Cancer Lett 205: 1-8, 2004.

18. https://indeks.mp.pl/leki/desc.php?id=752

19. Cuzick J, Powles T, Veronesi U, Forbes J, Edwards R, Ashley S and Boyle P: Overview of the main outcomes in breast-cancer prevention trials. Lancet 361: 296-300, 2003.

20. Nayfield SG, Karp JE, Ford LG, Dorr FA and Kramer BS: Potential role of tamoxifen in prevention of breast cancer. J Natl Cancer Inst 83: 1450-1459, 1991.

21. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, et al: Tamoxifen for prevention of breast cancer: Report of the national surgical adjuvant breast and bowel project P-1 Study. J Natl Cancer Inst 90: 1371-1388, 1998.

22. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90: 1371-1388, 1998.

23. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, Bevers TB, Kavanah MT, Atkins JN, Margolese RG, et al: Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 97: 1652-1662, 2005.

24. Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, et al; Italian Tamoxifen Study Group: Tamoxifen for the prevention of breast cancer: Late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 99: 727-737, 2007.

25. Cuzick J, Forbes JF, Sestak I, Cawthorn S, Hamed H, Holli K and Howell A; International Breast Cancer Intervention Study I Investigators: Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst 99: 272-282, 2007.
26. Cuzick J, Sestak I, Cawthorn S, Hamed H, Holli K, Howell A and Forbes JF; IBIS-I Investigators: Tamoxifen for prevention of breast cancer: Extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol 16: 67-75, 2015.
27. Akram M, Iqbal M, Daniyal M and Khan AU: Awareness and current knowledge of breast cancer. Biol Res 50: 33, 2017.
28. Tkaczuk-Włach J, Sobstyl M and Jakiel G: Rak piersi – znaczenie profilaktyki pierwotnej i wtórnej; Joanna Tkaczuk-Włach, Małgorzata Sobstyl, Grzegorz Jakiel. Przegl Menopauz 4: 343-347, 2012.
29. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 90: 1371-1388, 1998.
30. Waters EA, McNeel TS, Stevens WM and Freedman AN: Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010. Breast Cancer Res Treat 134: 875-880, 2012.
31. Li F, Dou J, Wei L, Li S and Liu J: The selective estrogen receptor modulators in breast cancer prevention. Cancer Chemother Pharmacol 77: 895-903, 2016.
32. Veronesi U, Maisonneuve P, Rotmensz N, Costa A, Sacchini V, Travaglini R, D'Aiuto G, Lovison F, Gucciardo G, Muraca MG, et al; Italian Tamoxifen Study Group: Italian randomized trial among women with hysterectomy: Tamoxifen and hormone-dependent breast cancer in high-risk women. J Natl Cancer Inst 95: 160-165, 2003.
33. Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, Costa A, Sacchini V, Travaglini R, D'Aiuto G, et al; Italian Tamoxifen Study Group: Tamoxifen for the prevention of breast cancer: Late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst 99: 727-737, 2007.
34. Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, Tidy A, Viggers J and Davey J: Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet 352: 98-101, 1998.

35. Powles TJ, Ashley S, Tidy A, Smith IE and Dowsett M: Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 99: 283-290, 2007.

36. Tamoxifen for prevention of breast cancer: Extended longterm follow-up of the IBIS-I breast cancer prevention trial; Jack Cuzick, Ivana Sestak, Simon Cawthorn, Hisham Hamed, Kaija Holli, Anthony Howell, John F Forbes, on behalf of the IBIS-I Investigators*. Lancet Oncol 16: 67-75, 2015.

37. https://www.mp.pl/onkologia/nowotwory/rak-piersi/zapobieganie/132062,tamoksyfen-w-prewencji-raka-piersi-odlegle-wyniki-badania-ibis-i.html

38. Ivana Sestak and Jack Cuzick; Update on breast cancer risk prediction and prevention

39. National Institute for Health and Care Excellence: Familial breast cancer: classification and care of people at risk of familial breast cancer and management of breast cancer and related risks in people with a family history of breast cancer. NICE, London, UK, 2013.

40. Tuttle TM, Habermann EB, Grund EH, Morris TJ and Virnig BA: Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. J Clin Oncol 25: 5203-5209, 2007.

41. Narod SA: Hormonal prevention of hereditary breast cancer. Ann N Y Acad Sci 952: 36-43, 2001.

42. Calderon-Margalit R and Paltiel O: Prevention of breast cancer in women who carry BRCA1 or BRCA2 mutations: A critical review of the literature. Int J Cancer 112: 357-364, 2004.

43. Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, Ellis NA, Boyd J, Borgen PI, Barakat RR, et al: Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 346: 1609-1615, 2002.

44. Kote-Jarai Z et al (2007) BRCA1/BRCA2 mutation status and analysis of cancer family history in participants of the Royal Marsden Hospital tamoxifen chemoprevention trial. Cancer Lett 247(2):259–265 18. Xu

45. King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, Tait J, Ford L, Dunn BK, Costantino J, et al; National Surgical Adjuvant Breast and Bowel Project: Tamoxifen and breast cancer incidence among women with inherited mutations in BRCA1 and BRCA2: National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial. JAMA 286: 2251-2256, 2001.

46. Xu L, Zhao Y, Chen Z, Wang Y, Chen L and Wang S: Tamoxifen and risk of contralateral breast cancer among women with inherited mutations in BRCA1 and BRCA2: A meta-analysis. Breast Cancer 22: 327-334, 2015.
47. Phillips KA, Milne RL, Rookus MA, Daly MB, Antoniou AC, Peock S, Frost D, Easton DF, Ellis S, Friedlander ML, et al: Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. J Clin Oncol 31: 3091-3099, 2013.
48. Akram M, Iqbal M, Daniyal M and Khan AU: Awareness and current knowledge of breast cancer. Biol Res 50: 33, 2017.
49. Jakubowska A and Gronwald J: Lubiński J i wsp. Rola tamoksifenu u nosicielek mutacji BRCA1 w chemoprewencji dziedzicznego raka piersi. Contemp Oncol (Pozn) 6: 597-601, 2002.
50. Phillips KA and Lindeman GJ: Breast cancer prevention for BRCA1 and BRCA2 mutation carriers: Is there a role for tamoxifen? Future Oncol 10: 499-502, 2014.
51. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 351: 1451-1467, 1998.
52. Maltoni C, et al: Experimental results on the chemopreventive and side effects of tamoxifen using a human-equivalent animal model. In: The scientific bases of cancer chemoprevention. Maltoni C, Soffritti M and Davis W (eds). Elsevier Science BV, Amsterdam, pp197-207, 1996.
53. Decensi A, Bonanni B, Guerrieri-Gonzaga A, Gandini S, Robertson C, Johansson H, Travaglini R, Sandri MT, Tessadrelli A, Farante G, et al: Biologic activity of tamoxifen at low doses in healthy women. J Natl Cancer Inst 90: 1461-1467, 1998.
54. Decensi A, Robertson C, Viale G, Pigatto F, Johansson H, Kisanga ER, Veronesi P, Torrisi R, Cazzaniga M, Mora S, et al: A randomized trial of low-dose tamoxifen on breast cancer proliferation and blood estrogenic biomarkers. J Natl Cancer Inst 95: 779-790, 2003.
55. de Lima GR, Facina G, Shida JY, Chein MB, Tanaka P, Dardes RC, Jordan VC and Gebrim LH: Effects of low dose tamoxifen on normal breast tissue from premenopausal women. Eur J Cancer 39: 891-898, 2003.