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REVIEW ARTICLE

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# The impact of combined oral contraception and hormone replacement therapy on breast cancer development

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## ABSTRACT

The assessment of breast cancer relative morbidity risk in women taking oral contraceptives (OC) or hormone replacement therapy (HRT) — currently known as menopausal hormone therapy — is still a challenge. The analysed groups of women vary widely depending on the type, route of application and doses of hormones, the duration of administration, and the time from therapy cessation. Moreover, the risk of breast cancer depends on the patient's genetic predisposition, and for this reason the analyses of OC and HRT should be performed separately in the group of healthy women, in *BRCA1/2* mutation carriers, and in breast cancer survivors. This paper was aimed to analyse the safety of OC and HRT in three groups of women depending on the risk of breast cancer development (healthy women) or breast cancer recurrence (breast cancer survivors).

**Key words:** oral contraceptives, hormone replacement therapy, menopausal hormone therapy, breast cancer

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## Introduction

Oestrogens are established mitogen factors affecting epithelial breast cells; however, their mechanism of action was recognised only recently. Initially it was thought that progestogens act on breast cells and endometrium in similar patterns; however, physiologically the highest proliferation of breast cells is observed during the luteal phase of the menstrual cycle, e.g. with high levels of oestrogens as well as progestogens. The proliferation rate, reflected by the Ki-67/MIB-1 level, is higher in patients taking oral contraceptives than in women with natural menstruation [1].

Although the molecular mechanisms of the carcinogenic effects of oral contraceptives (OC) and hormone replacement therapy (HRT) — the current name menopausal hormone therapy (MHT) — in breast are not completely understood, it seems that oestrogens and progestagens contribute to cancer promotion and acceleration of cancer manifestation. Hormones act on already abnormal epithelial breast cells and all steps of carcinogenesis are completed with the ultimate development of cancer and its manifestation during OC or HRT [2]. These suggestions are supported by the results of some trials showing that breast cancers are diagnosed usually one year after initiating of OC and HRT, but 10 years after cessation of therapy the risk returns to baseline [3, 4].

The assessment of breast cancer relative morbidity risk in women taking OC or HRT is a challenge. The analysed groups of women widely vary depending on the type of hormones used (oestrogens alone vs. oestrogens combined with progestogens), the route of their application [pills, transdermal patches, intra-uterine devise (IUD)] and dose, the duration of administration, and the time after therapy cessation. It should be underlined that the risk of breast cancer development should be analysed separately in the group of healthy women, in *BRCA1/2* mutation carriers, and in patients with breast cancer.

The aim of the study was to discuss the indications to OC and HRT in relation to the risk of breast cancer development (healthy women) or breast cancer progression (breast cancer patients). Additionally, the recommendations regarding the use of OC and HRT in different risk groups were presented.

**Table 1. Relative risk of breast cancer development after oral contraceptive**

| Stosowanie COC | Meta-analysis 1996 [14] | Meta-analysis 2013 [7] |
|---|---|---|
| | Relative risk | Relative risk |
| Currently using COC | 1.24 | 1.08 |
| 14 years after cessation | 1.16 | 1.21 |
| 5–9 years after cessation | 1.07 | 1.17 |
| 10–20 years after cessation | 1.01 | 1.13 |
| > 20 years after cessation | – | 1.02 |

COC — combined oral contraception

## Oral contraception and breast cancer

Combined oral contraception (COC), containing oestrogens and progestogens, is one way of family planning, and this has been used since the 1960s. Approximately 20% of women using contraception worldwide choose these pills. Among women in the age from 25 to 35 years this percentage is 33% [5], and in the Polish population it is approximately 39% [6].

The goal and the main benefit of using OC is the limitation of unintended pregnancies, but it also decreases the percentage of extrauterine pregnancies, ovarian cysts and ovarian cancers, endometriosis and endometrial cancer, as well as colorectal cancer (CRC) [7]. The protective role of OC in ovaries possibly results from inhibition of ovulation. On the other side, OC could simultaneously increase the risk of cardiovascular diseases, cervical cancer (particularly in HPV infected women) [7], and breast cancer [2, 8–13]. Increased production of coagulation proteins in the liver caused by oestrogens and unfavourable serum lipids profile related to progestagens, leads to a 3–4-fold increased risk of thromboembolic events (stroke in particular). Thromboembolic risk is especially high in women with additional factors of cardiovascular diseases risk, like smoking or suffering from migraines [9].

Taking into consideration that the risk of thromboembolic event and breast cancer development depends on the dose of oestrogens and progestagens, in the 1960s the daily dose of OC was decreased from 150 $\mu$g of mestranol to 20–35 $\mu$g of metynyloestradiol [9] and from 9.85 mg norethynodrel to less than 1 mg of different progestogens [14].

### Hormone contraception and the risk of breast cancer development in an unselected healthy female population

The very first meta-analysis of 54 studies, including 53.297 female breast cancer patients and 100.239 healthy women in 25 countries (90% of all available data concerning OC and breast cancer) was published in 1996, and it found that the relative risk (RR) of breast cancer development in women currently using OC was 1.24 ($p < 0.00001$) [14] and decreased together with prolongation of time since termination of OC. The risk after 1–4 years from OC cessation RR was 1.16, and after 5–9 years it was 1.07. No increased risk of breast cancer was noted after 10 years since permanent discontinuation of OC.

In 2007 an updated meta-analysis of current clinical trials was published (studies with lower hormone doses were included) [15]. Relative risk of breast cancer development in women using OC at any time was 1.19, and it was higher in women taking OC before first-term pregnancy (1.44), than in women after pregnancy (1.15). This observation supports the unfavourable influence of OC on breast before its development process is finished and shows the need for careful observation of very young women using OC. Fortunately, the absolute increase of breast cancer morbidity was very low, resulting from a low rate noted in young women.

A meta-analysis of over 100 non-randomised clinical trials evaluating correlation between OC and the development of different cancers, including 44 studies with breast cancer patients, was published in 2013 and confirmed numerically low, but statistically important, increasing of risk of breast cancer development (HR = 1.08) [7]. Table 1 summarises the results of the meta-analyses.

In conclusion, the analysis of unselected cohorts of healthy women indicated that oral hormone contraception in currently used low doses is correlated with slightly increased risk of breast cancer development.

### Hormone contraception in healthy women with family history of breast/ovarian cancer and in *BRCA1/2* mutation carriers

The study including women with positive family history of breast/ovarian cancer, taking OC before 1975 in a dose exceeding 50 $\mu$g of ethinyloestradiol per day, indicated a 3–11-fold increased risk of breast cancer development, proportionally to the number of family members suffering from this cancer [16]. In 2009 a meta-analysis of 12 clinical studies with OC in women with positive family history of breast cancer was published, which indicated increased risk of breast cancer development only in the subgroup of women taking OC before

1975. This correlation was not observed in women using more modern hormonal formulations [17–19].

The risk of breast cancer development in patients with *BRCA1* and *BRCA2* gene mutations, who use OC, is still a matter of controversy [20, 21]. A meta-analysis of 18 clinical trials, including women with *BRCA1/2* gene mutations, published in 2010, indicated that the relative risk in women taking OC before 1975 was 1.47, but in women using newer hormone pillsit was lower (RR = 1.17) [13]. There were no differences between carriers of *BRCA1* and *BRCA2* gene mutations (RR = 1.09 and RR = 1.15, respectively). To note, OC decreased risk of ovarian cancer (RR = 0.50) and this protective effect intensified with time [13]. This is important information for physicians involved in genetic counselling, who present the risks and benefits of OC and HRT use to healthy carriers of *BRCA1/2* gene mutations, who are at very high risk of breast cancer and ovarian cancer development.

There are no consistent statements from the World Health Organisation (WHO) and the American College of Obstetricians and Gynaecologists (ACOG) regarding the use of oral contraception in relation to the risk of breast cancer development. According to the WHO recommendations, using of OC do not increase the risk of breast cancer development in healthy women with positive family history and/or carrying germinal mutations known to be related to breast cancer [19]. According to the ACOG, positive family history regarding breast cancer is not a contraindication to use of OC. However, patients with *BRCA1/2* gene mutations are at higher risk of breast cancer development if they are using OC for more than five years before 30 years of age, with simultaneously decreased risk of ovarian cancer development [19].

## Hormone contraception in women with breast cancer

According to the evidence regarding breast cancer pathophysiology, the WHO does not recommend hormone contraceptive methods in patients with this cancer, because of the risk of disease recurrence and intensification of thromboembolic complications [22]. Patients with breast cancer are advised to use hormone-free intrauterine contraception. There is no consensus regarding a uniform opinion about the safety of intrauterine contraception with progestogens (levonorgestrel) in that group of patients [23].

## Who is the best candidate for hormone contraception?

As the risk of breast cancer development is not consistent in overall female population, the decision regarding using of OC should be based on individualized analysis of benefits and risks related to hormones. Women should review together with physician all risk factors for breast cancer development (life style — alcohol consumption and obesity; reproduction — age of menarche and first childbirth as well as breastfeeding) as well as inherited predisposition to breast cancer development (family history regarding breast/ovarian cancer, carrying state of *BRCA1/2* mutations) [24]. Additionally, the history regarding cardiovascular diseases (tobacco smoking, hypertension, diabetes, heart failure, cerebrovascular diseases, migraine, family history regarding myocardial infarction, thrombosis, lung embolism, stroke and inherited coagulation disorders, levels of serum cholesterol fractions) should be taken and individual risk should be established.

The woman deciding to use OC should be informed about danger of tobacco smoking (increases the risk of thromboembolic complications), advised about regular gynecological visits together with cervical cytology and examination of breasts in order to early diagnose potential abnormalities [12]. Healthy women could use OC till menopause or, after finishing of procreation period the contraception method could be change [10]. In women with migraine and smokers the termination of OC in 35 year of age should be discussed, as after this the risk of thromboembolic complications is significantly increased. There is no data regarding the risk of OC complications in very young women, so there is difficult to establish appropriate period of OC use in this subgroup. The women with heart failure, coronary artery disease, cerebrovascular diseases and breast cancer should be advised to use other contraception method.

Healthy women, carriers of *BRCA1/2* genes mutations should be familiarized with increased risk of breast cancer development after OC, particularly if it is used longer than 5 years in younger age, before the first pregnancy. The decision regarding OC usage should be made after consultation of genetic counselling centres. Given the significant controversies regarding the risk of using OC by carriers of *BRCA1/2* genes mutations, some genetic counselling centres advise not to use this contraception method.

## Hormone contraception — summary

1. Modern, low-dose, oral hormone contraception used in healthy women with average risk of breast cancer and cardiovascular diseases remains safe and efficient birth control method. In these populations the risk of breast cancer development is low.
2. Using of oral hormone contraceptives in health female carriers of *BRCA1*/*BRCA2* gene mutations is still the subject of controversial debate taking into consideration increased risk of breast cancer

development and decreased risk of ovarian cancer mortality.

3. Oral hormone contraception is not recommended in breast cancer patients. It is suggested using another method of birth control in this population (intra-uterine device, IUD).

## Hormone replacement therapy (menopausal hormone therapy) and breast cancer

### Hormone replacement therapy (menopausal hormone therapy) and a risk of breast cancer in unselected healthy women population

Hormone replacement therapy (HRT), currently known as menopausal hormone therapy (MHT), was initially introduced in order to control vasomotor symptoms of menopause, since estrogens administration is the most efficient way to alleviate most common abnormalities (hot flushes, night sweats, tachycardia, headache and dizziness, fatigue, anxiety, depression, sleep disorders) as well as genitourinary symptoms, connected to epithelial atrophy (vaginal dryness and itching, increased frequency of urination [pollakiuria]). Sixty years after HRT introducing, perimenopausal symptoms still remain the most important justification of its use, particularly in women before 60 years or during first 10 years after menopause [25–28].

The second indication to HRT is fracture prevention during osteoporosis, especially in women before 60 years or during first 10 years after menopause [25–29]. However, HRT is not recommended in all patients with osteoporosis, regarding side effects and availability of other effective methods for treatment of this disease. HRT could be used in selected patients, with failure after alternative drugs administration.

As 5-fold increasing of the risk of endometrial cancer development was revealed as one of the side effects of estrogens administration, since '70s of last century progestogens were added to estrogens, hereby initiating the era of combined, two-component estrogen–progrestagen hormone replacement therapy [30].

In 1997 meta-analysis was performed, including 51 clinical trials presenting correlations between HRT and a risk of breast cancer development. Evaluated studies comprised approximately 90% of available scientific literature regarding this topic. The analysis included 53.865 postmenopausal women, of whom 17.830 (33%) had used HRT [31]. In women using HRT for 5 years or longer the relative risk of breast cancer development was increased (RR = 1.35). Five years after HRT cessation breast cancer risk returned back to baseline.

In cohort Million Women Study [32], including over 1 million women participated in breast cancer skreening, the relative risk of breast cancer development in women currently using HRT was 1.66 ($p < 0.0001$), and the risk of death due to breast cancer was 1.22 ($p = 0.05$). It was no increased risk of breast cancer development in women previously using HRT (RR = 1.01). Relative risk of breast cancer was significantly higher in women taking estrogens combined with progestogens (RR = 2.0, $p < 0.0001$) as compared to women taking estrogens alone (RR = 1.30, $p < 0.0001$). Absolute risk of breast cancer development after the use of estrogens combined with progestogens was 6/1000, and after estrogens alone 1.5/1000 (Table 2).

The most important clinical trials addressing the role of HRT in breast cancer development were 2 randomized studies, conducted by Women's Health Initiative (WHI) in 40 sites in United States [33–45]. The first trial analysed the role of estrogens alone (conjugated equine estrogens in daily dose of 0.625 mg vs. placebo) in women after hysterectomy (10.739 women), and the second one was aimed to assess the role of estrogens and progestagens (conjugated equine estrogens in daily dose of 0.625 mg and medroxyprogesterone acetate in daily dose of 2.5 mg vs. placebo) in women with reproductive organs preserved (16.608 women). The eligible women were in the age range of 50–79 age and they were recruited between 1993–1998. The study arm with two-component HRT was closed after 5.6 years and with estrogens alone after 7.2 years.

After 11 years of follow-up it was showen, that women receiving estrogens alone had a decreased risk

**Table 2. Relative risk of breast cancer development in women using hormone replacement therapy in the Million Women Study [51]**

| Duration of HRT | Relative risk (95% CI) |
|---|---|
| Never using HRT | 1.00 (0.96–1.04) |
| Previously using HRT: | |
| shorter than 1 year | 0.94 (0.84–1.05) |
| 1–4 years | 1.01 (0.92–1.12) |
| 5–9 years | 1.14 (1.00–1.30) |
| 10 years and longer | 1.05 (0.84–1.30) |
| Currently using oestrogens alone: | |
| shorter than 1 year | 0.81 (0.55–1.20) |
| 1–4 years | 1.25 (1.10–1.41) |
| 5–9 years | 1.32 (1.20–1.46) |
| 10 years and long | 1.37 (1.22–1.54) |
| Currently using oestrogens with progestogens: | |
| shorter than 1 year | 1.45 (1.19–1.78) |
| 1–4 year | 1.74 (1.60–1.89) |
| 5–9 years | 2.17 (2.03–2.33) |
| 10 years and long | 2.31 (2.08–2.56) |

HRT — hormone replacement therapy; CI — confidence interval

of breast cancer development (HR = 0.77, p = 0.02) and also the risk of death due to breast cancer (HR = 0.37, p = 0.03) as compared to placebo [44]. Contrary to this, the women taking estrogens combined with progestogens had a increased risk of breast cancer development comparing to placebo (HR = 1.55, p < 0.001) and slightly increased risk of death due to breast cancer (HR = 1.32), however this difference was not statistically significant (p = 0.15) (Table 3) [43].

In 2013 up-dated results of WHI studies were published after 13 years of follow-up [45]. They confirmed the increased risk of breast cancer development after two-component HRT (HR = 1.28, p < 0.001), although it was slightly lower than during previous analyses of this population. Additionally, comparing to placebo group decreased risk of breast cancer development was still seen (HR = 0.79). Mechanism of these differences was not explained until now (Table 4).

**Table 3. Influence of hormone replacement therapy women health (based on the randomised clinical study Women's Health Initiative [33–43])**

| Disease | Combined HRT (oestrogens/progestogens) | | Oestrogens alone HRT | |
|---|---|---|---|---|
| | Morbidity risk (HR) | Death risk (HR) | Morbidity risk (HR) | Death risk (HR) |
| Invasive breast cancer | 1.55 | 1.32 | 0.77 | 0.37 |
| Colorectal cancer | 0.75 | 1.54 | 1.11 | 0.99 |
| Non-small cell lung cancer | 1.23 | 1.71 | 1.17 | 0.89 |
| Endometrial cancer | 0.78 | | 1.08 | |
| Ovarian cancer | 1.58 | | – | |
| Cervical cancer | 1.44 | | – | |
| Ischaemic heart disease | 1.22 | | 0.95 | |
| Stroke | 1.34 | | 1.36 | |
| Deep venous thrombosis | 1.88 | | 1.47 | |
| Pulmonary embolism | 1.98 | | 1.37 | |
| Cholelithiasis/cholecystitis | 1.61 | | 1.79 | |
| Urinary incontinence | 1.39 | | 1.53 | |
| Dementia | 2.05 | | 1.49 | |
| Bone fracture | 0.76 | | 0.70 | |

HRT — hormone replacement therapy; HR — hazard ratio

**Table 4. Updated results of the randomised *Women's Health Initiative* study after 13 years of follow-up [44, 45]**

| Disease | Combined HRT (oestrogens/progestogens) | | Oestrogens alone HRT | |
|---|---|---|---|---|
| | Morbidity risk (HR) | p | Morbidity risk (HR) | p |
| Invasive breast cancer | 1.28 | < 0.01 | 0.79 | 0.02 |
| Colorectal cancer | 0.80 | 0.06 | 1.13 | 0.39 |
| Non-small cell lung cancer | 1.10 | 0.38 | 0.98 | 0.87 |
| Endometrial cancer | 0.67 | 0.01 | – | |
| Ovarian cancer | 1.24 | 0.30 | – | |
| Coronary heart disease | 1.09 | 0.19 | 0.94 | 0.43 |
| Stroke | 1.16 | 0.06 | 1.15 | 0.10 |
| Deep venous thrombosis | 1.24 | 0.40 | 1.05 | 0.71 |
| Pulmonary embolism | 1.26 | 0.05 | 1.15 | 0.34 |
| Bone fracture | 0.81 | 0.02 | 0.91 | 0.44 |
| Death for any reason | 0.99 | 0.87 | 0.99 | 0.92 |
| Death from cardiovascular reasons | 0.97 | 0.73 | 0.97 | 0.75 |
| Cancer-related deaths | 1.07 | 0.32 | 0.95 | 0.58 |

HR — hazard ratio

Published in 2012 Cochrane meta-analysis of 23 clinical trials including 42.830 women receiving either HRT or placebo confirmed the increased risk of breast cancer development after combined estrogens–progesteron therapy, but statistically significant increase of breast cancer development after estrogens alone was not shown [28].

## Hormone replacement therapy (menopausal hormone therapy) in healthy women as prevention of cardiovascular disease

Based on over 40 publications presenting beneficial effect of HRT on cardiovascular system and skeleton as well as general well-being, HRT started to become widely used in primary and secondary prevention of neurocognitive disorders and demention during '80s and '90s of last century. Additionally the time period of HRT administration was prolonged from 1–2 years (typical duration of HRT for menopausal symptoms control) up to 5–10 years or even longer [46]. However, randomized WHI clinical studies [33] did not confirm protective role of HRT on cardiovascular system. Increased risk of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism was noted. Beneficial influence of HRT on brain efficiency was also not confirmed.

Based on this and other studies [28, 29, 33] it was established, that two-component HRT should not be neither recommended nor continued in prevention of ischaemic heart disease (Table 3 and 4).

## Hormone replacement therapy (menopausal hormone therapy)in patients with diagnosis of cardiovascular diseases

Randomized HERS (Heart and Estrogen/Progestin Replacement Study) clinical study [47] analysed the influence of combined HRT on the clinical course of ischaemic heart disease in 2763 women with previously diagnosed cardiovascular disease. This study did not confirm protective role of HRT, it was even shown higher percentage of cardiac complications in this female population [48]. During 6.8 years of follow-up in HERS II clinical trial [48] no decrease in the risk of cardiovascular complications in women with ischaemic heart disease using HRT was shown (RR = 0.99).

Cochrane meta-analysis of 23 clinical trials including 42830 women receiving either HRT or placebo — published in 2012 — confirmed the increased risk of thromboembolic complications after combined estrogen–progesteron therapy in women with cardiovascular diseases [28]. Based on foregoing results HRT is not recommended for using in order to decrease of ischaemic heart disease risk in cardiovascular disease patients [25–27].

## Who is the best candidate to hormone replacement therapy/menopausal hormone therapy?

In 2012–2013 the indications for HRT were updated. According to the U.S. Preventive ServicesTask Force [29], the U.S. Food and Drug Administration [25], the International Menopause Society, and seven other scientific societies (the American Society for Reproductive Medicine, the Asia Pacific Menopause Federation, the Endocrine Society, the European Menopause and Andropause Society, the International Menopause Society, the International Osteoporosis Foundation, and the North American Society) [26] and the British Menopause Society [27], the most important indications for HRT are vasomotor symptoms of menopause; less frequently it is indicated for the prevention of fracture resulted from osteoporosis in patients with high risk of fracture, not tolerating other treatment options.

Before initiation of HRT healthy women should be informed in detail about the risk-benefit balance related to the preparations used, and the individual cumulative risk should be estimated. Detailed medical history should also be considered with special attention to risk factors of breast cancer development and cardiovascular disease. The final decision regarding HRT should be made by the patient based on risk-benefit assessment.

The exact time period of HRT administration has not been established to date. It is determined on an individual basis, depending on intensity of symptoms and individual risk of complications (thromboembolic disease, stroke, ischaemic heart disease, and breast cancer) [26, 27]. In healthy women, who have no significant increase in the risk of breast cancer and cardiovascular diseases, the duration of HRT should be limited to the period with maintenance of menopausal symptoms. The risk-benefit ratio should be repeatedly assessed after each therapy year, and based on this the decision about continuation or termination of HRT should be made. Total therapy time period should be as short as possible.

## Hormone replacement therapy (menopausal hormone therapy) in breast cancer patients

There is only sparse scientific evidence regarding the risk of cancer recurrence and death after HRT in women with breast cancer.

In 2006 a pooled analysis of 15 clinical trials was published, including seven controlled studies, which involved 1416 female patients with breast cancer using HRT [49]. The analysis showed that HRT does not increase the risk of disease recurrence and death due to cancer in this population.

To date there have been two randomised clinical trials only analysing the risk of HRT in breast cancer

patients. The HABITS study enrolled 447 patients. This trial was stopped after interim analysis showing a doubling of the disease recurrence (HR = 2.4) [50]. Final risk [51] was 3.5-fold higher as compared with women not receiving HRT. The second randomised Stockholm study indicated a higher risk of second breast cancer (HR = 3.6), despite initial suggestions regarding lack of risk of primary cancer progression (HR = 0.82) [52].

Since 2013 eight scientific societies (the International Menopause Society, the American Society for Reproductive Medicine, the Asia Pacific Menopause Federation, the Endocrine Society, the European Menopause and Andropause Society, the International Menopause Society, the International Osteoporosis Foundation, andthe North American Society) have not recommended HRT in patients with current or recent breast cancer [26].

The present statement is much more restrictive than previous versions, in which the use of trial HRT in breast cancer patients with intense menopausal symptoms was permitted for 1–3 months and could be continued for 1–2 years in case of clinical improvement. However, the patient had to be informed about and accept a 30% increasing of the risk of breast cancer recurrence. Current publications do not contain such a recommendation.

## Hormone replacement therapy — summary

1. The most important indication to HRT in healthy women are vasomotor menopausal symptoms. Hormone replacement is the most effective method of preventing and managing such complaints.
2. The second indication to HRT is the treatment and prevention of osteoporosis in selected patients, with failure after other drugs.
3. Hormone repalacement therapy should not be used for primary and secondary prevention of cardiovascular diseases because there is no preventive effect for cardiovascular disease. Oestrogens and progestogens increase the risk of stroke, pulmonary embolism, and thromboembolic disease. There is also no evidence that HRT is efficient if prevention of neurocognitive disorders and dementia.
4. Combined oestrogen–progestogen HRT increases the risk of breast cancer development in healthy women, whereas oestrogens alone decrease this risk.
5. Genetic counselling centres advise against the use of HRT by healthy carriers of *BRCA1/2* gene mutations, because of the cumulative risk of breast cancer development and cardiovascular disease, related to strong hereditary predisposition to this cancer and age.
6. HRT is not recommended in breast cancer patients.

Figures 1 and 2 presentsthe current statement regarding use of OC and HRT in connection with breast cancer.

## Alternative methodsof vasomotor symptoms reduction

Many non-hormone treatment methods were evaluated with regard to reducing vasomotor symptomsof menopause, but only a few of them delivered any clinical benefit. Up to now the following methods have been studied: lifestyle modification (physical exercise), phytoestrogen-rich diet (soy), non-hormone drugs (selective serotonin reuptake inhibitors, SSRIs, and serotonin-norepinephrine reuptake inhibitors, SNRIs, gabapentin), behavioural therapy (cognitive behavioural therapy, relaxation techniques, yoga),as well as alternative medicine (acupuncture) [53, 54]. Analyses of numerous non-randomised trials as well as meta-analyses indicated that currently there is a lack of evidence confirming the efficacy of physical exercise, phytoestrogen-rich diet, or dietary supplements in reducing of vasomotor symptoms of menopause [53]. Similarly, too few publications dedicated to behavioural therapy and alternative medicine make their efficacy impossible to assess.

SSRIs, SNRIs, and gabapentin are the most efficient in reducing of vasomotor symptoms, especially hot flushes [53, 54]. Drugs from the SSRI group (paroxetine,

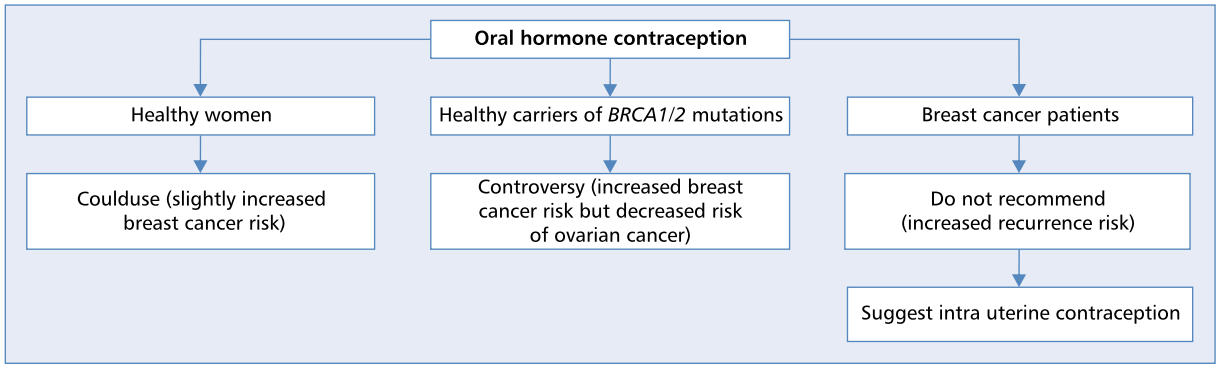


**Figure 1.** Principles of oral contraception depending on the risk of breast cancer development in young women — oral hormone contraception

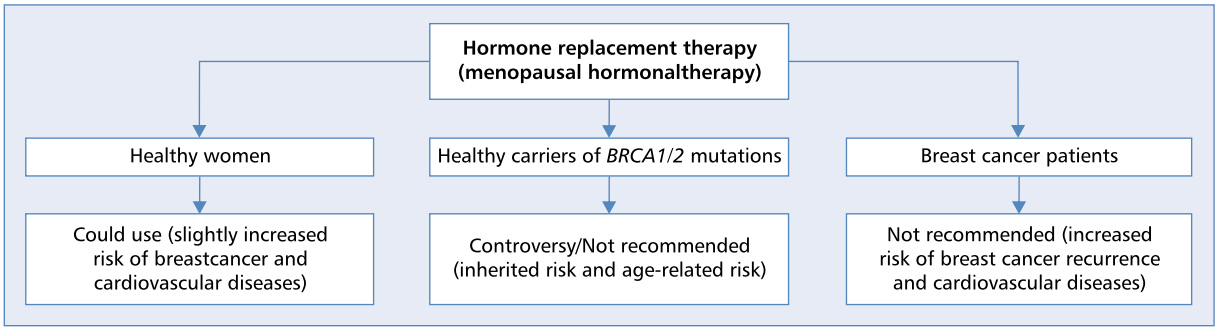


**Figure 2.** Principles of oral contraception depending on the risk of breast cancer development in peri- and postmenopausal women — hormone replacement therapy

escitalopram, citalopram, and sertraline) sufficiently decrease the frequency and intensity of hot flushes, and paroxetine is the most potent drug out of them. Venlafaxine (SNRI) were also shown to effectively treat menopausal symptoms, together with the most frequent like lack of appetite, nausea, and constipation. *Gabapentin, a gamma*-aminobutyric acid (GABA) analogue, is also effective in alleviating of menopausal and other symptoms due to tamoxifen administration; however, dizziness, heart palpitations, fatigue, and peripheral oedema are very frequent side effects. Alpha-2 adrenergic receptor agonist, clonidine, is another drug used in patients with hot flushes, but it results in dry mouth, constipation, and sleep disorders. Beta-blockers reduce anxiety and heart palpitations, but with no influence on hot flushes. All pharmacological methods mentioned above were evaluated in the treatment of hot flushes not only in healthy women but also in patients with breast cancer. Despite the effectiveness in a portion of the women, none of them was as effective as hormone preparations [53].

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