

Preventative therapies for healthy women at high risk of breast cancer

Ivana Sestak

Centre for Cancer Prevention,
Wolfson Institute of Preventive
Medicine, Queen Mary University
of London, Charterhouse Square,
London, UK

Abstract: Tamoxifen has been shown to reduce the risk of developing estrogen receptor (ER)-positive breast cancer by at least 50%, in both pre- and postmenopausal women. The current challenge is to find new agents with fewer side effects and to find agents that are specifically suitable for premenopausal women with ER-negative breast cancer. Other selective estrogen receptor modulators (SERMs), such as raloxifene, arzoxifene, and lasofoxifene, have been shown to reduce the incidence of breast cancer by 50%–80%. SERMs are interesting agents for the prevention of breast cancer, but longer follow-up is needed for some of them for a complete risk–benefit profile of these drugs. Aromatase inhibitors have emerged as new drugs in the prevention setting for postmenopausal women. In the Mammary Prevention 3 (MAP3) trial, a 65% reduction in invasive breast cancer with exemestane was observed, and the Breast Cancer Intervention Study-II trial, which compared anastrozole with placebo, reported a 60% reduction in those cancers. Although SERMs and aromatase inhibitors have been proven to be excellent agents in the preventive setting specifically for postmenopausal women and ER-positive breast cancer, newer agents have to be found specifically for ER-negative breast cancers, which mostly occur in premenopausal women.

Keywords: breast cancer, preventive therapy, selective estrogen receptor modulators, aromatase inhibitors, high-risk women

Introduction

Breast cancer is by far the most common cancer in women worldwide, with an estimated 1.67 million new cancers diagnosed in 2012.¹ Breast cancer is associated with a variety of lifestyle choices, such as obesity, later onset of first childbirth, and the use of hormone replacement therapy, which is also increasing in the developing world. Breast cancer still remains the second cause of cancer death in the developed world. There has been a trend toward reduction of breast cancer mortality, due to advanced early detection and better therapeutic strategies. However, breast cancer incidence and mortality have remained extremely high.

The identification of women who are at high risk of developing the disease, which typically means a 5-year breast cancer risk of 1.67% or higher, is key to chemoprevention of breast cancer. Traditionally, women are categorized as being high risk for breast cancer due to their family history. However, new developments in the ability to predict and modify breast cancer risk have been found. One example is mammographic density, which in terms of population attributable risk, accounts for more breast cancers than family history.² Targeting women at high risk of developing breast cancer identified by biomarkers, such as breast density, atypical hyperplasia, or lobular carcinoma in situ,

Correspondence: Ivana Sestak
Centre for Cancer Prevention, Wolfson
Institute of Preventive Medicine,
Queen Mary University of London,
Charterhouse Square, London EC1M
6BQ, UK
Email i.sestak@qmul.ac.uk

with a high population attributable risk,³ and offering them agents that reduce their risk of developing the disease are likely to lead the way in developing this approach to cancer prevention.

Chemoprevention is the use of drugs, vitamins, food supplements, vaccines, or other agents to try to reduce the risk, delay the development, or recurrence of cancer, and it is a promising strategy for cancer prevention.⁴ It is therefore crucial to identify as precisely as possible which types of breast cancers can be prevented by specific agents.

Here, a comprehensive review of breast cancer prevention approaches for women at high risk of developing the disease will be presented. Most will be dedicated to the discussion of selective estrogen receptor modulators (SERMs), of which tamoxifen is the most widely studied and has been used in the past few decades to treat breast cancer; and it has also been shown to reduce the incidence of invasive breast cancer. Furthermore, results have been reported on aromatase inhibitors (AIs) for breast cancer prevention in women at high risk of the disease, which will also be discussed in this overview.

Selective estrogen receptor modulators

SERMs are chemically diverse compounds with the capability to bind to estrogen receptors (ERs). They have both selective agonist and antagonist abilities on a variety of organs, which contain ERs.

Tamoxifen

Tamoxifen is a well-known and extensively researched compound. Tamoxifen has been adapted for application in both the treatment and prevention of breast cancer.^{5,6} Four major prevention trials⁷⁻¹⁵ have been completed and published updated results on the use of tamoxifen as a preventive agent (Table 1). Overall, a reduction of 38% in the risk of breast cancer has been observed.⁶ Although no effect on breast cancers with ER-negative origin has been observed, the results from an overview of all the trials suggest that 50% of ER-positive breast cancers can be prevented with 5 years of active tamoxifen use. The updated results from the SERM overview have reported that an extended beneficial effect of tamoxifen is observed even after 5 years of treatment completion.¹⁶

Although tamoxifen has been proven to significantly reduce the incidence of breast cancer, increases in endometrial cancer and venous thromboembolic events are the most serious adverse events of this drug. Overall, both adverse

events were increased between 2 and 2.5 fold in tamoxifen users, but analysis of long-term follow-up data has shown that thromboembolic events were not in excess after tamoxifen treatment was stopped.¹⁰ In summary, tamoxifen prevents ER-positive breast cancer during the first 5 years of treatment and also after treatment cessation. The benefits could persist even longer, and therefore tamoxifen is an attractive chemopreventive option, specifically in premenopausal women, where life expectancy is long.

Raloxifene

Raloxifene is also a SERM developed for the prevention of osteoporosis in postmenopausal women. Like tamoxifen, it has both estrogen-agonistic effects on the bone and lipid metabolisms and estrogen-antagonistic effects on the endometrial and breast tissues. All the studies investigating raloxifene as a preventive agent for the reduction in breast cancer incidence were initially developed as osteoporosis or cardiovascular prevention trials, and breast cancer incidence was a secondary endpoint.

Four trials have reported their results using raloxifene as a preventive agent (Table 1). Both the Multiple Outcomes of Raloxifene Evaluation¹⁷ and the Continuing Outcomes Relevant to Evista¹⁸ reported a significant reduction (65% and 50%, respectively) in breast cancer overall. Like tamoxifen, an increase in thromboembolic events has been observed with raloxifene, but no significant excess in endometrial cancers or other gynecological problems has been found.

Another study was the Raloxifene Use for The Heart study,¹⁹ where an overall reduction of 44% for invasive breast cancer was found with raloxifene, which is similar in size to that seen for tamoxifen in other studies. A direct comparison between tamoxifen and raloxifene was performed in the Study of Tamoxifen and Raloxifene trial.²⁰ The efficacy was about 25% lower for raloxifene compared with tamoxifen, but there were fewer thromboembolic events and gynecological problems with raloxifene. Although raloxifene is widely used in the prevention of osteoporosis, its use in the preventive setting for breast cancer is not common.

Other SERMs

Two other SERMs (lasofoxifene and arzoxifene) have been investigated in postmenopausal women. The PEARL (Postmenopausal Evaluation and Risk Reduction With Lasofoxifene) trial recruited 8,556 postmenopausal healthy women to three treatment arms: placebo versus 0.25 mg/day lasofoxifene versus 0.5 mg/day lasofoxifene for 5 years in a 1:1:1 ratio (Table 1).²¹

Table 1 Details of breast cancer prevention trials

	N	Recruitment period	Treatment groups and daily dose	Treatment duration (years)	Entry criteria	Present status	Median follow-up (months)
Marsden ^{7,8}	2,471	1986–96	Placebo (1,233) Tamoxifen 20 mg (1,238)	5–8	High risk, family history	Blinded, further follow-up	171.6 (153.9–184.0)
IBIS-1 ^{9,10}	7,109	1992–2001	Placebo (3,566) Tamoxifen 20 mg (3,573)	5	>2-fold relative risk	Blinded, further follow-up	96 (80.1–117.1)
NSABP-P1 ^{13,14}	13,205	1992–97	Placebo (6,707) Tamoxifen 20 mg (6,681)	5	>1.6% 5-year risk	Unblinded, no follow-up	57.6 (35.4–64.9)
Italian ^{11,12,15}	5,048	1992–97	Placebo (2,708) Tamoxifen 20 mg (2,700)	5	Normal risk, women with hysterectomy	Unblinded, further follow-up	139.6 (122.0–146.1)
MORE ¹⁷ /CORE ¹⁸	7,705/6,511	1994-98/1998-2002	Placebo (2,576) Raloxifene 60 mg (2,557)/ Placebo (2,576) Raloxifene 120 mg (2,572)	4/8	Normal risk, postmenopausal women with osteoporosis	Unblinded, no follow-up	71.3 (47.1–95.4)
RUTH ¹⁹	10,101	1998–2000	Placebo (5,057) Raloxifene 60 mg (5,044)	5	Normal risk, postmenopausal women with established or risk of CHD	Unblinded, no follow-up	66.7 (60.1–72.3)
STAR ²⁰	19,490	1999–2004	Raloxifene 60 mg (9,875) Tamoxifen 20 mg (9,872)	5	>1.6% 5-year risk, postmenopausal women	Unblinded, no follow-up	81 (60.8–96.6)
PEARL ²¹	8,856	2001–07	Placebo (2,852) Lasofoxifene 0.50 mg (2,852) Lasofoxifene 0.25 mg (2,852)	5	Normal risk, postmenopausal women with osteoporosis	Blinded, no follow-up	59.6 (58.8–60.1)
GENERATIONS ²²	9,354	2004–09	Placebo (4,678) Arzoxifene 20 mg (4,676)	4	Normal risk, postmenopausal with low BMD or osteoporosis	Unblinded, no follow-up	54.3 (28.3–56.1)

Note: Trials are sorted according to agent and recruitment period. Reprinted with permission from Elsevier (*The Lancet*, 2013;381:1827–1834, Cuzick J, Sestak I, Bonanni B, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data).¹⁶

Abbreviations: IBIS, International Breast cancer Intervention Study; MORE, Multiple Outcomes of Raloxifene Evaluation; CORE, Continuing Outcomes Relevant to Evista; RUTH, Raloxifene Use for The Heart; STAR, Study of Tamoxifen And Raloxifene; CHD, coronary heart disease; BMD, bone mineral density; PEARL, Postmenopausal Evaluation and Risk Reduction With Lasofoxifene; FU, follow-up.

All breast cancers (including ductal carcinoma in situ [DCIS]) were significantly reduced by 0.5 mg/day lasofoxifene when compared to placebo, whereas no significant effect was seen for women receiving 0.25 mg/day lasofoxifene, although a beneficial trend was seen. An even greater reduction was seen for invasive ER-positive breast cancer with 0.5 mg/day lasofoxifene. Furthermore, lasofoxifene significantly reduced major coronary events, strokes, and both vertebral and non-vertebral fractures, so may be ideal for prevention where the total benefit/harm balance is particularly important. Overall, there were no differences between the groups in terms of other serious adverse events.

The GENERATIONS trial evaluated the effect of arzoxifene (20 mg/day) versus placebo in 9,354 postmenopausal women with osteoporosis (Table 1).²² Arzoxifene reduced all breast cancer occurrences by 58%. The incidence of DCIS was substantially but nonsignificantly reduced. Arzoxifene

also reduced vertebral fractures by 41% but an increase was seen for thromboembolic events, hot flushes, muscle cramps, and gynecological events.

A recently published SERM overview¹⁶ is the only comprehensive analysis of all SERM prevention trials to date. The meta-analysis reported on a substantial update on all SERM trials with long-term follow-up (except for the arzoxifene and lasofoxifene trials) and the results clearly showed that all SERMs significantly reduce the incidence on invasive ER-positive breast cancer (Figure 1). However, as seen in all individual trials as well, no effect of SERMs was seen for ER-negative breast cancers, and it is clear that new approaches have to be found to reduce the incidence of these cancers in a high-risk population. Another important finding was that benefits from SERMs were not only seen during the active 5 years of follow-up but also after treatment was completed, indicating a long-term effect of SERMs in the prevention of

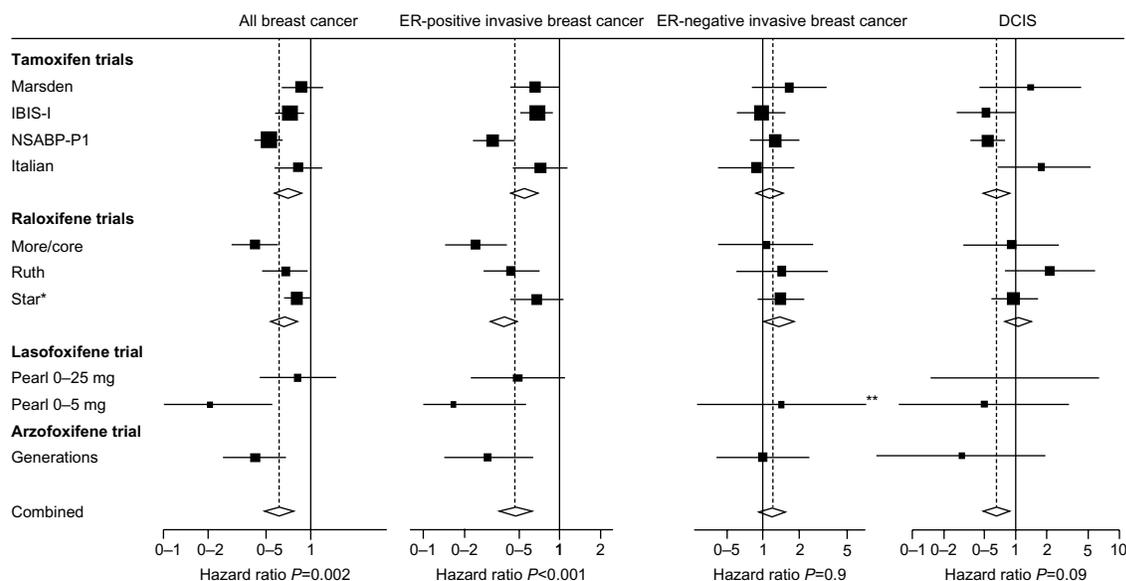


Figure 1 Forest plots for all breast cancer, ER+/ER- invasive breast cancer, and DCIS according to SERM and trial.

Notes: *Adjusted by overall tamoxifen effect to give raloxifene vs placebo comparison, STAR data not included in overall effect; **pooled data. Reprinted with permission from Elsevier (*The Lancet*, 2013;381:1827–1834, Cuzick J, Sestak I, Bonanni B, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data).¹⁶

Abbreviations: ER, estrogen receptor; IBIS, International Breast cancer Intervention Study; MORE, Multiple Outcomes of Raloxifene Evaluation; CORE, Continuing Outcomes Relevant to Evista; RUTH, Raloxifene Use for The Heart; STAR, Study of Tamoxifen And Raloxifene; ER, estrogen receptor; SERM, selective estrogen receptor modulator; DCIS, ductal carcinoma in situ; PEARL, Postmenopausal Evaluation and Risk Reduction With Lasofoxifene.

breast cancer. The decision to use a SERM for breast cancer prevention should not solely be based on the effect on breast cancer incidence. Adverse effects, notably thromboembolic events and, for tamoxifen only, endometrial cancers, have to be taken into account when assessing the risk–benefit ratio for each individual patient. This decision making is a very complex, individual, and complicated matter, but an improved risk–benefit ratio for SERMs might be indicated for women who are at high risk of breast cancer at any age compared to those with average risk. However, currently, the only chemopreventive option for premenopausal women is tamoxifen. Recently, in the UK, the National Institute for Health and Care Excellence has published updated guidelines for the use of tamoxifen (and raloxifene) for women at high risk of developing breast cancer, although these drugs are not licensed for this purpose in the UK.²³

Aromatase inhibitors

Third-generation AIs (anastrozole, letrozole, and exemestane) act via the inhibition of the cytochrome P450 enzyme aromatase, which converts androgens into estrogens.²⁴ In metastatic disease, many trials have shown that AIs have great benefits when compared to megestrol acetate. Most of the use of AIs in the preventive setting derives from adjuvant studies in postmenopausal women with early breast cancer.

Adjuvant trials

The use of AIs has been widely investigated in postmenopausal women with early breast cancer (Table 1).^{25–30} Several different study designs have been investigated, and most trials used the AI as an initial treatment,²⁷ some used it after 2–3 years of tamoxifen,^{26,28,30} or as an extended treatment after 5 years of tamoxifen use.^{29,31} All these trials, irrespective of the study design, have shown a consistent reduction in contralateral breast cancer. Specifically, the Anastrozole, Tamoxifen, Alone or in Combination trial showed that 5 years of anastrozole use significantly improved disease-free survival when compared to tamoxifen,^{25,32–34} and the updated results confirmed the better efficacy of anastrozole over tamoxifen as initial adjuvant treatment in postmenopausal women with early breast cancer.³³

Based on these findings, AIs are being routinely used in the treatment of breast cancer. Furthermore, a recently conducted meta-analysis of adjuvant trials with AIs indicated that these agents consistently showed lower recurrence rates when compared to tamoxifen, either as initial therapy or after 2–3 years of tamoxifen use.³⁵ This overview provides clear evidence that AIs achieve significant reductions in breast cancer recurrence.

Prevention trials

The use of AIs in the preventive setting has not yet been extensively investigated. Two main prevention trials have

reported their results to date. The Mammary Prevention 3 (MAP3) trial compared the steroidal AI exemestane with placebo in postmenopausal women at increased risk of breast cancer, whereas the International Breast cancer Intervention Study-II (IBIS-II) trial investigated the use of anastrozole in a similar population.

The MAP3 trial enrolled over 4,500 postmenopausal women who were at risk of developing breast cancer and randomized them to either exemestane or placebo for 5 years. After a median of 35 months of follow-up, 11 invasive breast cancers were found with exemestane versus 32 with placebo, resulting in a 65% reduction of invasive breast cancers with exemestane.³⁶ No effect was seen for ER-negative disease. No statistically significant differences were found between treatment arms for adverse events, suggesting a good risk–benefit profile. However, this trial had some limitations, most importantly the short follow-up period of only 35 months. Due to this immaturity, the MAP3 trial does not allow for any conclusion of the safety and long-term efficacy of this drug. Furthermore, after publications of the results, women on placebo were offered the opportunity to cross-over to exemestane, which does not permit the assessment of long-term efficacy of this drug, including overall, and specifically, breast cancer mortality.

The IBIS-II trial compares anastrozole with placebo in postmenopausal women at increased risk of breast cancer. The main results were recently reported after a median of 5 years of follow-up,³⁷ and a highly significant reduction of invasive ER-positive breast cancers was seen with anastrozole compared with placebo in this high-risk population (58%, HR = 0.42 [0.25–0.71]), which was similar to the results reported in the MAP3 trial. As in the MAP3 trial, no effect of anastrozole was found for ER-negative breast cancer. Vasomotor and musculoskeletal side effects were increased with the use of anastrozole, and these side effects were also reported by many women on placebo. Strengths of the IBIS-II trial were the large number of breast cancers reported and the median follow-up of 5 years. All women remain blinded for long-term follow-up, which is important since overall long-term efficacy of anastrozole, or any other AI, for healthy postmenopausal women at increased risk of breast cancer has not yet been established.

Overall, the reported reductions for both exemestane and anastrozole were larger than those seen for tamoxifen or any other SERMs, and these results indicate that both drugs are attractive options for breast cancer prevention in postmenopausal women at increased risk of the disease. For premenopausal women, the only option remains tamoxifen. Tamoxifen, exemestane, and anastrozole are all out of patent,

and registering these drugs for use in the preventive setting will most probably not be marketed. Although approved by several regulatory authorities for the use in the preventive setting, these drugs, despite their effectiveness, are unfortunately not widely accepted as breast cancer preventive drugs by high-risk women and their physicians. Reasons for the low uptake of chemopreventive agents, SERMs or AIs, are fear of side effects, general practitioners not being aware of chemopreventive options for high-risk women, and the drug industry not promoting the drugs for primary prevention.

Other agents

Other agents have emerged, although initially developed for other diseases, which might be useful for the prevention of breast cancer in high-risk women. New generations of chemopreventive agents that do not modulate the endocrine pathways have been studied recently.

Metformin

Metformin is a safe drug widely used by millions of people for the treatment of non-insulin-dependent diabetes. It works by targeting the enzyme AMP-activated protein kinase, which induces muscles to take up glucose from the blood. The rationale for the use of metformin in breast cancer prevention comes from obesity being an independent risk factor for breast cancer in postmenopausal women. Many studies have shown that long-term use of metformin may have a beneficial effect on breast cancer risk. Small biomarker studies in women with breast cancer in a placebo-controlled setting are ongoing and these results may lead to larger chemoprevention trials with metformin.

Bisphosphonates

Bisphosphonates were originally developed for the treatment of osteoporosis and are commonly used in the breast cancer setting in controlling bone loss induced by AIs and chemotherapy. In addition, adjuvant breast cancer trials evaluating the oral bisphosphonate clodronate suggested a reduction in cancer recurrence, but the findings were mixed.³⁸ Several studies have now shown that bisphosphonates reduce breast cancer in postmenopausal women by around 30%.^{38,39} These findings require a cautious interpretation since bisphosphonates are given to women with a low bone mineral density and these women are at a decreased risk of breast cancer. However, these agents are well tolerated, and primary prevention trials are needed to fully investigate the risk–benefit ratio of these agents for breast cancer prevention. It is not clear if they are suitable for premenopausal women.

Nonsteroidal anti-inflammatory drugs

Long-term follow-up of randomized trials using aspirin in the prevention of vascular disease showed that daily use reduced the incidence of colorectal cancer and several other cancers. Evidence from case-control and cohort studies indicates a reduction of breast cancer risk by about 10% for aspirin and possibly a little more for ibuprofen.^{40,41} Similar results have been found with other nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors.⁴² Although an effect of NSAIDs on breast cancer risk reduction is too small to make a conclusive decision regarding its sole use in the prevention of breast cancer, these drugs may be part of a broad intervention approach, specifically since a beneficial effect is seen on colorectal cancers and cardiovascular disease.⁴³

The IBIS-III trial will integrate several chemopreventive agents in one trial. This trial will directly address the issue of late recurrence in postmenopausal breast cancer survivors and will include integrated biological studies to explore mechanisms of drug action and to identify which patients are at greatest risk of late recurrence. Specifically, this trial will attempt to determine which cancers are most susceptible to control with metformin and/or an AI and/or a bisphosphonate in a 2×2×2 factorial trial. Of particular interest will be any possible positive synergism between these agents.

Conclusion

The prevention of ER-positive breast cancer with SERMs is well established, and they are the only option for premenopausal women to date. However, despite their efficacy, these drugs have not been well accepted as preventive agents by high-risk women or clinicians, mostly because of adverse events. For postmenopausal women, the AIs have been established for the treatment of breast cancer and recent publications also favor those drugs over SERMs in the preventive setting. Both the MAP3 and IBIS-II trials have reported a significant reduction for invasive breast cancer in postmenopausal women in the preventive setting.

Biomarkers are important for the identification of women at high risk, and breast density is currently the most attractive measure. Breast density is a well-established risk factor for breast cancer and it has been shown that change in breast density might predict drug effectiveness and therefore be a useful surrogate marker.⁴⁴ Similarly, a recent publication has reported that mammographic density during the use of adjuvant endocrine treatment was a significant predictor for recurrence in women with ER-positive breast cancer.⁴⁵

The prevention of incidence or recurrence of ER-negative disease remains a huge challenge, and other agents have to be developed for the prevention of these tumors. Recent research interests have been in so-called non-endocrine-based pathways, such as epidermal growth factor 1 or human epidermal growth factor. NSAIDs,⁴⁶ COX-2 inhibitors,^{47,48} retinoids, rexinoids, and statins^{49,50} may also protect against both receptor positive and receptor negative tumors, but results only from observational studies or adjuvant studies are available at the moment, and there are still inconsistencies. A new agent, deguelin, which prevents mammary tumorigenesis, has shown important advances in the prevention of ER-negative breast cancer.⁵¹

Of great interest are the single nucleotide polymorphisms (SNIPs) that individually have minor effects of risk but are common. Some women will have several of these SNIPs to have an impact on their breast cancer risk, especially in combination with mammographic density and other known factors. An assessment of how SNIPs might improve risk assessment among high-risk women is needed for better targeting of preventive therapy. In a recent study, Cuzick et al evaluated a panel of 15 SNIPs and found that they are useful for refining risk estimates in women at high risk of developing breast cancer.⁵²

In conclusion, there are many options for the prevention of ER-positive breast cancer, specifically in postmenopausal women who can be given a SERM or an AI. For premenopausal women, only tamoxifen can be potentially used as a preventive agent as AIs are not indicated in this group of women. It remains unclear how to prevent the incidence of ER-negative breast cancer, which occurs mostly in premenopausal women, and more research is needed to specifically target this unsolved matter.

Disclosure

The author reports no conflicts of interest in this work.

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