Hormone Replacement Therapy Appears to Be Safe After Prophylactic Adnexectomy in Premenopausal BRCA1/BRCA2 Mutation Carriers

Reaction to the 'Letter to readers' in Hereditary Cancer in Clinical Practice, 2005, 3 (2)

Jan Lubiński

In writing the letter to readers of our journal three months ago I was asking about opinions concerning the use of hormone replacement therapy (HRT) in BRCA1/2 carriers after prophylactic adnexectomy, because at that time it was practically impossible to present **evidence-based recommendations**. Actually, most of the responses we have received have been opinions. It is important to recognise that the situation is now much clearer with studies performed by Tim Rebbeck et al which are to be published in the **Journal of Clinical Oncology**. The following responses have been received:

Prof. Henry T. Lynch, Creighton's Hereditary Cancer Institute; Department of Preventive Medicine, Creighton University School of Medicine, Omaha, NE, USA, htlynch@creighton.edu

My opinion about the use of HRT following prophylactic surgeries in BRCA1 carriers remains a bit controversial. Many confounders enter into the decision making category. Most important is, in my opinion, whether or not the patient has had any prior evidence of carcinoma of the breast, age of onset, and of course, whether there is so-called benign pathology showing proliferative disease with atypia.

I remain reluctant to advise HRT for any patients with BRCA1 (or BRCA2 for that matter), unless the woman is having significant postmenopausal type problems, wherein quality of life becomes a major issue.

Prof. Dr. Rita Schmutzler, Abt. Molekulare Gynäko-Onkologie, Universitäts-Frauenklinik, Cologne, Germany, rita.schmutzler@uk-koeln.de

As a coordinator of the German Hereditary Breast and Ovarian Cancer Consortium I would like to contribute our current strategy on HRT after prophylactic salpingo-oophorectomy (PSO).

1. We advise PSO after completion of child-bearing around the age of 40.
2. Most mutation carriers decide to have this procedure. The exact numbers will be available soon.
3. We advise women that it may be beneficial to abstain from HRT and that PSO without HRT may result in an even higher risk reduction for breast cancer (50% with HRT according to the Kauff and Rebbeck data) although no clear data are available yet.
4. We discuss that we may substitute hormones if postmenopausal complaints are unacceptable and decrease quality of life considerably. Therefore we see the patients on a regular basis after PSO in order to record and discuss the side effects and provide psychological support.
5. We also offer participation in the IBIS2 trial (prospective randomised trial on aromatase inhibitor (AI) versus placebo).
6. In case of participation in the IBIS trial or abstention from HRT we check osteoporosis risk factors and may offer a Dexa scan possibly followed by bisphosphonate substitution.
7. If patients do not want to be randomised and prefer an additional medical prevention we offer tamoxifen.

Monique M.A. Brood-van Zanten, Marius J. van der Mooren, René H.M. Verheijen, Peter Kenemans, Department of Obstetrics & Gynaecology, VU University Medical Center, Amsterdam, the Netherlands

Experimental data on the effects of hormone therapy (HT) in women with BRCA1/2 mutations are not available. HT is effective for flushes and vaginal dryness. Theoretical models have calculated that use of HT until the age of 50 after pBSO in women with

BRCA1/2 mutations is associated with small changes in life expectancy [1]. Colditz et al [2] found that HT use does not further increase the risk of breast cancer in high-risk women. HT should not be prescribed for longer than 5 years.

Breast density increases with combined oestrogen/progestogen use, but does not change or increases slightly with oestrogen alone or tibolone. A possible excess risk for breast cancer in high-risk women with pBSO induced by HT is unknown.

Women who undergo pBSO are at risk of primary peritoneal cancer, and it remains to be determined whether HRT influences the risk of peritoneal cancer in carriers of BRCA mutations.

Considerations

BRCA1/2 mutation and ER- status

BRCA1-related breast cancers are more frequently oestrogen receptor (ER) negative than are either BRCA2-related or non-hereditary breast cancers [3]. In particular, breast cancers occurring in older BRCA1 carriers are much more likely to be ER-negative than are breast cancers developing in older non-carriers. Only 3.9% of BRCA1-related breast cancers were ER-positive cancers occurring in women in their postmenopausal years.

BRCA1/2 mutation and mammography

Breast density is high in women with a family history of breast cancer [4]. Breast cancers are more difficult to detect in dense breast tissue.

There is a high prevalence of premalignant lesions in BRCA1/2 carriers, especially after the age of 40 [5]. Mammography does not detect high-risk histopathological lesions [6].

BRCA1/2 mutation and OC use

Among BRCA2 mutation carriers, use of oral contraceptives was not associated with an increased risk of breast cancer [7]. Compared with BRCA1 mutation carriers who never used oral contraceptives, those who used oral contraceptives for at least 5 years had an increased risk of breast cancer, although it appears that oral contraceptive use after the age of 30 is not likely to increase the risk of breast cancer among BRCA1 mutation carriers [8]. However, OC is associated with a risk reduction for ovarian cancer [9], possibly due to altered hormone receptor function [10].

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Following risk-reducing bilateral salpingo-oophorectomy (BSO), a woman carrying a BRCA1 or

BRCA2, without a personal history of breast cancer, should make an informed personal decision about the use of hormone replacement therapy (HRT), based on her age, menopausal symptoms and personal/family medical history. Overall, I believe that HRT post risk-reducing BSO is not contraindicated under the age of 50 years; however, there are some difficulties interpreting the literature. Oophorectomy prior to menopause may be associated with a number of adverse effects including significant menopausal symptoms, unfavourable changes in lipid profile, an increased risk of cardiovascular disease and an increased risk of osteoporosis. I advise women that the use of low dose HRT, until the age of 50, will not increase their prior risk of breast cancer because HRT will provide less oestrogen than her ovaries would have provided up until the age of natural menopause. The literature also suggests that HRT does not negate the 50% breast cancer risk reduction associated with premenopausal BSO [1]. The use of HRT following risk-reducing BSO is also supported by a recent decision analysis. The model showed that prophylactic oophorectomy, in women carrying a BRCA1/2 mutation, lengthened life expectancy by 3.34 to 4.65 years, depending on the age of oophorectomy; and that the use of HRT showed very small reductions in the life expectancy gains [2]. The fact that no data are available about the actual affect of HRT on breast cancer risk in BRCA1/2 carriers is one limitation of this model [3]. Data from the Women's Health Initiative (WHI) suggest that the increased risk of breast cancer appears to be limited to those receiving combined HRT [4]; however, the option of hysterectomy and unopposed oestrogen in premenopausal BRCA1/2 mutation carriers is controversial because there is insufficient evidence to support this recommendation. Although most BRCA1/2 mutation carriers over the age of 50 will avoid HRT, some enquire about the short-term use of HRT for relief of menopausal symptoms. The Women's Health Initiative (WHI) concludes that short-term HRT is not associated with a significantly increased risk of breast cancer; however, the ability to extrapolate these data to BRCA1/2 mutation carriers remains unclear.

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Judy Kirk, Director, Familial Cancer Service, Westmead Hospital, Sydney NSW, Australia

At the Familial Cancer Service at Westmead, our advice to such women has evolved over the past ten years. There is now good evidence that risk-reducing salpingo-oophorectomy (RRSO) before the menopause reduces the risk of both ovarian/fallopian tube cancer and also of breast cancer. For this reason, our unaffected female BRCA1/2 carriers are now strongly advised that RRSO (+/- risk reducing mastectomy) is the best option available at the current time to reduce cancer risk. They are also informed of the lack of proven efficacy of screening for ovarian cancer. RRSO is suggested at the age of 35-40 for BRCA1 gene mutation carriers, but is generally deferred until the age of 40-45 in the case of BRCA2. This advice needs to be individualised for carriers already affected by breast cancer, depending on their age, time since diagnosis and disease prognosis. RRSO may also be considered to provide adjuvant therapy for pre-menopausal BRCA carriers with a recent diagnosis of hormone-dependant breast cancer.

In the period from 1996 until the present, we have identified 34 BRCA1 carriers who are now aged ≥35 (suitable for RRSO), and who had one or both ovaries intact at the time they received their genetic test result. Of these, 44% have taken up the option of RRSO since knowing their genetic status. Over the same time, 9 (36%) of 25 BRCA2 carriers now aged ≥40, with ovaries intact at genetic testing, have taken up RRSO. These figures include some women for whom a diagnosis of breast cancer in the previous 5 years may have impacted upon their decision. The uptake of RRSO over the whole ten years is about 40% overall, but on review, this has not increased recently, even with the giving of stronger clinical advice.

In BRCA carriers choosing RRSO, who are unaffected by breast cancer, the option of post-operative HRT should be discussed. We agree with Lubiński that there is no evidence that HRT in such cases is contra-indicated, though non-hormonal

alternatives can also be trialled in these women. Management can be tailored to address specific symptoms, such as hot flushes or vaginal dryness.

In Australia, over 12,000 individuals from almost 1000 high-risk breast/ovarian cancer kindreds are currently enrolled in the national collaborative kConFab (Kathleen Cuningham Foundation CONsortium for research into FAmilial Breast cancer) study. The study may eventually help to address the question of safety and efficacy of HRT in high-risk women. Importantly, the participants in the study have indicated that provision of information about management of symptoms following pre-menopausal RRSO is an important issue for them. In response, kConFab and Dr Peter Grant (Melbourne) have addressed this need in a recent newsletter sent to all participants (http://www.kconfab.org – see winter 2005 newsletter).

Prof. Shirley Hodgson, St George's Hospital Medical School, London, United Kingdom, shodgson@sgul.ac.uk

Usually we suggest oophorectomy with salpingectomy ... on the whole I think many people do give replacement oestrogens.

Lenka Foretova, Masaryk Memorial Cancer Institute, Brno, Czech Republic, foretova@mou.cz

We have observed a low level of acceptance of preventive adnexectomy in our BRCA1/2 carriers, who are receiving follow-up in our high-risk clinic. All of those women are informed by medical geneticists and by gynaecologists about their increased risk of ovarian cancer and about the problems with early detection and are offered prophylactic surgery between 35 and 40 years of age. Only 40% of those eligible women finally opt for surgical prevention. The reasons are mostly the fear of complications in their marriage, in their sexual life and other well-recognised problems with oestrogen deficiency. In cases of continued refusal the patients are asked to sign a 'declaration' to indemnify the gynaecologist.

The gynaecologist evaluates all women individually and offers the HRT only to those who really need it. Livial (tibolon) is a replacement choice, which may have only a small effect on breast cancer risk.

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I think it is essential to base such discussions on data, not on opinions. We have both data and

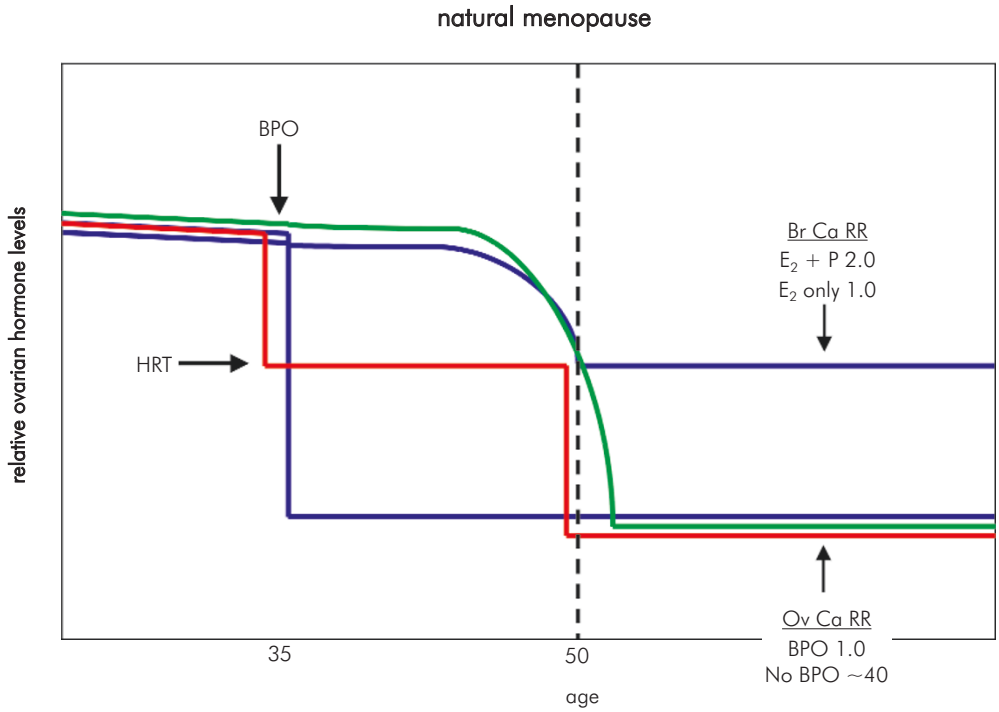

Fig. 1. Hormone replacement after premenopausal oopherectomy

a rationale to support the hypothesis that HRT (particularly unopposed oestrogen) is safe for these women, and MOST CERTAINLY safer than delaying oophorectomy because of concerns about symptoms of menopause. It is particularly important to note that women with BRCA1 mutations who have intact ovaries are not only at very high risk of developing ovarian cancer, and substantially higher risk of breast cancer than such women after oophorectomy, but producing more ovarian hormones than provided by replacement doses. I will send you a copy of our paper that has been recently accepted by JCO. Enclosed please find a slide explaining the rationale for this (Fig. 1).

Timothy R. Rebbeck, Ph.D., Jill E. Stopfer, M.S., CGC, Susan Domchek, M.D.

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COMMENTARY: USE OF HORMONE REPLACEMENT THERAPY AFTER BILATERAL RISK-REDUCING OOPHORECTOMY IN *BRCA1* AND *BRCA2* MUTATION CARRIERS

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Bilateral risk-reducing oophorectomy (BRRO) is widely used for cancer risk reduction in women with *BRCA1/2* mutations. BRRO significantly reduces breast cancer risk by approximately 50% [1, 2] and ovarian cancer risk by 85-95% [2-4]. An immediate consequence of BRRO in premenopausal women is the induction of surgical menopause, which can result in severe hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and cognitive changes that may affect quality of life [5]. Premature menopause is a significant risk factor for osteoporosis [6]. Thus, some premenopausal women who undergo BRRO elect to use at least short-term HRT to alleviate these symptoms. Other mutation carriers may delay BRRO because of concerns about HRT and breast cancer risk and remain at high risk for ovarian cancer. As there are multiple studies suggesting that HRT, particularly combined oestrogen-progesterone use, increases risk of breast cancer in postmenopausal women [7], there is legitimate concern that HRT may offset the breast cancer risk reduction conferred by BRRO.

Importantly, these studies of HRT in postmenopausal women are not directly applicable to premenopausal women undergoing BRRO. For example, the median age of the participants in the Women's Health Initiative (WHI) was over 60, well past the average age of menopause in the United States, and participants were included who had previously taken HRT [7, 8]. Most importantly, the participants in the WHI were not selected for premature menopause, and the vast majority underwent non-surgical menopause. Despite these limitations, the results of the WHI study are widely known to patients and physicians and have led to a dramatic reduction in the use of hormone replacement in postmenopausal women in the United States [9]. However, the results of the WHI need to be interpreted with caution when counselling BRCA1/2 mutation carriers undergoing premature, surgically induced menopause for risk reduction purposes.

Recently we reported that HRT of any type after BRRO did *not* significantly alter the reduction in breast cancer risk associated with BRRO in *BRCA1/2* mutation carriers. In this study, we prospectively examined 462 women with *BRCA1/2* mutations and evaluated breast cancer risk after BRRO with or without any HRT [3]. BRRO was associated with a significantly lower risk of breast cancer (HR=0.40, 95% CI: 0.18-0.92) which was not altered by the use of HRT (risk of breast cancer HR=0.37, 95% CI: 0.14-0.96). These results suggested that short-term HRT use does not negate the protective effect of BRRO on subsequent breast cancer risk in *BRCA1/2* mutation carriers. While unanswered questions remain regarding the use of HRT after BRRO, such as the optimal type, duration and timing of HRT, it is now possible to make reasonable decisions about clinical management of women with *BRCA1/2* mutations who have undergone BRRO.

Surgical type and its influence on post-surgery HRT use

A number of options are available to women with *BRCA1/2* mutations who are considering surgical risk reduction. These include: a) bilateral salpingo-oophorectomy (BSO) alone with combined oestrogen/progesterone replacement; b) BSO alone with short-term oestrogen only replacement, considering the potential for an increased risk of uterine cancer; c) total abdominal hysterectomy (TAH) with BSO, followed by use of unopposed oestrogen; d) BSO with or without TAH and without HRT.

There are numerous considerations to be made when deciding among these and other possible interventions. Women who carry *BRCA1/2* mutations

may wish to weigh the risks and benefits of TAH at the time of BRRO using the following four considerations: 1) impact on HRT decisions; 2) uterine and cervical cancer risk; 3) impact on decisions regarding tamoxifen; 4) fallopian tube carcinoma risk.

First, TAH allows women who are unaffected by breast cancer to use unopposed oestrogen replacement therapy rather than combined oestrogen plus progesterone replacement therapy. This decision has implications for the use of total abdominal hysterectomy (TAH) at the time of BRRO, as use of unopposed oestrogen in the absence of hysterectomy is associated with an increased risk of endometrial cancer (RR=2.3, 95% CI 2.1-2.5) [10]. Recent data from the WHI demonstrated a significantly increased risk of breast cancer among postmenopausal women who took oestrogen and progesterone (HR=1.26, 95% CI 1.00-1.59) [7], but not among women who took oestrogen alone (HR=0.77, 95% CI 0.59-1.01) [8]. This difference is also supported by the results of the Million Women Study, which found a two-fold increase in breast cancer risk for users of oestrogen and progesterone (RR=2.00, 95% CI 1.89-2.12) but a significantly lower risk for users of oestrogen alone (RR=1.30, 95% CI 1.21-1.40) [11]. The effect of unopposed oestrogen vs. combined oestrogen and progesterone has not been well characterized in *BRCA1/2* mutation carriers, but based on the risk of oestrogen and progesterone in the Million Women Study, and the difference in the effect of oestrogen alone compared to oestrogen and progesterone in the WHI, the addition of progesterone remains a concern. Therefore, undergoing a TAH at the time of BRRO allows the use of oestrogen alone for HRT, which minimizes potential breast cancer risk and eliminates the endometrial cancer risk associated with unopposed oestrogen exposure.

Second, a number of reports suggest there is an increased uterine and possibly cervical cancer risk in *BRCA1/2* mutation carriers (uterine cancer RR=2.65, 95% CI 1.69-4.16; cervical cancer RR=3.72, 95% CI 2.26-6.10) [12, 13]. Even though early detection of these cancers is often possible, women already planning to undergo BRRO may consider whether they wish to eliminate uterine and cervical cancer risks by undergoing TAH at the time of their BRRO.

Third, tamoxifen has been shown to decrease the risk of contralateral breast cancer in *BRCA1/2* mutation carriers (OR=0.50, 95% CI 0.28-0.89) [14]. Therefore, tamoxifen use for prevention of breast cancer is a consideration for *BRCA1/2* mutation carriers who have completed HRT or who are not candidates for HRT. The reported increased uterine cancer risk associated with tamoxifen [15] is an additional consideration for women contemplating TAH.

Fourth, there is an excess risk of fallopian tube carcinoma in *BRCA1/2* mutation carriers compared to the general population with an estimated relative risk of over 100 [16]. Because a remnant of the fallopian tube is left in the uterine wall at the time of BSO without TAH, there is a theoretical benefit in considering TAH. However, the absolute lifetime risk for the development of fallopian tube cancer in mutation carriers is small (estimated at 3%) and there is currently very little information about the occurrence of fallopian tube cancer among women who have undergone BRRO without TAH.

If women consider having TAH in addition to BRRO, the added risk and recovery time from TAH should be considered. BRRO is an acceptable option in part because surgical risks and recovery time are outweighed by the benefit of a marked breast and ovarian cancer risk reduction. However, the risk benefit ratio for TAH in addition to BRRO is more complex, both due to the small absolute advantages of TAH and the potential for slightly higher morbidity associated with this procedure. All of these elements must be factored into the patient's decision about the surgical approach to cancer risk reduction. Women who are likely to benefit most from having a TAH at the time of BRRO are unaffected premenopausal women who will also be faced with decisions on HRT and future tamoxifen use. Women who are already postmenopausal or who have had breast cancer will not be considering issues of HRT and in these women the potential benefits of TAH are likely to be very small.

Type and timing of post-BPO HRT use

Many women who undergo premenopausal BRRO take HRT only until the age when they would have experienced natural menopause, generally the age of 50. Since risk reduction for breast cancer increases the earlier a woman has BRRO [2], many women consider timing this surgery after childbearing decisions are completed, often in their mid to late 30's. Our recent study [3] supports the decision to use short-term HRT to manage immediate post-operative menopausal symptoms, but does not address the potential that long-term use may have very different implications for breast cancer risk than long-term hormone exposure in postmenopausal women. Furthermore, these results are consistent with the results of a recent decision analysis using hormone-associated risk data from the recently published Women's Health Initiative which suggests that short-term use of HRT after premenopausal BRRO is associated with little change

in life expectancy, whereas the impact of long-term use after the age of 50 is more substantial [17].

Recommendations

Based upon the literature available to date, women with *BRCA1/2* mutations should be discouraged from deferring BRRO because of fear of symptoms related to surgical menopause and should be reassured that use of short-term hormone replacement, if needed to manage menopausal symptoms, does not negate the breast cancer risk reduction from BRRO. BRRO, even with short-term HRT, results in dramatic reductions in both breast and ovarian cancer risk.

Acknowledgements

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