Breast Cancer Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

aHR = adjusted HR; **HER** = human epidermal growth factor receptor; **HR** = hazard ratio; **HRT** = hormone replacement therapy; **RR** = relative risk; **OS** = overall survival; **SERM** = selective estrogen receptor modulator.

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Welcome to Issue 25 of Breast Cancer Research Review.

A large Danish nationwide prospective cohort study has shown an increased risk of breast cancer in current and recent users of hormonal contraception versus women who have never used such contraception, with the risk increasing with duration of contraception use. They also found that the varying types of contraceptive pills had similar relative risks of breast cancer, including those containing progestins. Following on, we review an interesting randomised trial investigating Tibetan yoga for patients with breast cancer undergoing chemotherapy and discover beneficial effects. Other topics in this issue include physical activity and cognitive functioning in breast cancer survivors, neoadjuvant versus adjuvant chemotherapy in early breast cancer, tumour-infiltrating lymphocytes in different breast cancer subtypes, extended adjuvant intermittent versus continuous letrozole, and eribulin plus gemcitabine in HER2-negative metastatic breast cancer.

We hope you find this issue stimulating reading and welcome your feedback.

Kind Regards,

Dr Hilary Martin

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Contemporary hormonal contraception and the risk of breast cancer

Authors: Mørch LS et al.

Summary: This Danish nationwide prospective cohort study enrolled all women aged 15-49 years without cancer or venous thromboembolism or treatment for infertility (n = 1.8 million; 19.6 million person-years) to determine the relationship between hormonal contraception and risk of invasive breast cancer. In total, 11,517 cases of breast cancer occurred; the RR was 1.20 (95% CI 1.14-1.26) in all current and recent users of hormonal contraception versus women who had never used hormonal contraception. The risk increased from 1.09 (95% CI 0.96-1.23) with <1 year of use to 1.38 (95% CI 1.26-1.51) with more than 10 years of use (p = 0.002). The risk of breast cancer was still higher after discontinuation in those receiving hormonal contraceptives for ≥5 years. RR with current or recent use of various oral combination contraceptives (oestrogen-progestin) ranged from 1.0 to 1.6. Current or recent use of the progestin-only intrauterine system also carried a higher risk of breast cancer (RR 1.21; 95% CI 1.11-1.33). The overall absolute increase in current and recent users of any hormonal contraceptive was 13/100,000 person-years (95% CI 10-16), or one per 7690 women receiving hormonal contraception for 1 year.

Comment: This study investigates the association between the newer hormonal contraceptives including the levonorgestrel-releasing intrauterine system, contraceptive patches, vaginal rings, progestin-only implants and injections. The influence of progestin has been of particular interest given the association between the use of progestin and an increased risk of breast cancer in postmenopausal women on HRT. Progestins used as contraceptives include norethisterone, levonorgestrel and desogestrel. This study showed an RR of breast cancer with the use of hormonal contraception of 1.20 (95% CI 1.14-1.26) with the risk increasing with duration of use of contraception. The varying types of contraceptive pills had similar RRs including those containing progestins. The risk of breast cancer was also very similar to the overall group with the levonorgestrel-releasing intrauterine system with an RR of 1.21 (95% CI 1.11 to 1.33). Only a few breast cancer events occurred in those with the progestin-only implant and depot medroxyprogesterone acetate; however, it should be noted that the total number of people using these contraceptives was low. Based on this study it appears that progestins do not seem to increase the risk of breast cancer development above the risk of non-progestin-based contraceptive medications. Additional research is required to confirm the low event rates found in this study for the progestin-only implant and depot medroxyprogesterone acetate to determine whether these agents are associated with a lower RR of recurrence than other forms of hormonal contraception.

Reference: N Engl J Med. 2017;377(23):2228-39

Abstract

Randomized trial of Tibetan yoga in patients with breast cancer undergoing chemotherapy

Authors: Chaoul A et al.

Summary: This randomised trial studied effects on sleep and fatigue of Tibetan yoga versus stretching (4 sessions during chemotherapy followed by 3 booster sessions over 6 months and practice at home) or usual care in women with breast cancer undergoing chemotherapy. Total sleep disturbances and fatigue levels did not differ between treatment groups. Yoga participants reported fewer daily sleep disturbances (Pittsburgh Sleep Quality Index; PSQI) 1 week after treatment than stretching participants (difference -0.43; 95% CI -0.82 to -0.04; p = 0.03]) and usual care patients (difference -0.41; 95% CI -0.77 to -0.05; p = 0.02). Group differences at 3, 6 and 12 months were maintained for yoga versus stretching. Actigraphy data showed more minutes awake after sleep onset 1 week after treatment in stretching versus yoga (difference 15.36; 95% CI 7.25-23.48; p = 0.0003) and usual care (difference 14.48; 95% CI 7.09-21.87; p = 0.0002) recipients. Yoga participants who practiced ≥2 times/week during follow-up had better PSQI and actigraphy outcomes at 3 and 6 months after treatment.

Comment: Difficulty with sleeping is a common concern raised by patients. This contributes to patient fatigue and can impact on quality of life, function and mental health. This study compared the use of a Tibetan yoga program, a stretching program and usual care. Tibetan yoga has four main components 1) guided meditation 2) an alternate nostril breathing practice 3) Tsa lung movements which involve rotations and stretches of different body parts with accompanying specific breathing patterns and 4) compassion-based meditation. The stretching program included exercises recommended for women who are being treated for, or are recovering from breast cancer treatment and were similar to the movements in the Tibetan yoga programme (TYP). No statistically significant differences between groups were found for total sleep disturbance or fatigue. Patients in the TYP group did, however, have fewer daily disturbances of sleep 1 week after treatment than the other two groups. At longer-term follow-up, those who practiced the TYP ≥2 times/week had better sleep outcomes compared to those who did not, and compared with the usual care group at 3 and 6 months after completion of the program. Therefore it seems such a program appears to have a greater benefit for sleep in the longer term, rather than during chemotherapy treatment. Those in the stretching group appeared to have worse outcomes for sleep than the usual care arm. The reason for this is not identified. On the basis of this study, the stretching program should not be advised to assist with sleep, however, TYP could be advised though the benefits are likely to be greater following completion of chemotherapy rather than during active treatment.

Reference: Cancer 2018;124(1):36-45
Abstract

Randomized controlled trial of increasing physical activity on objectively measured and self-reported cognitive functioning among breast cancer survivors: The memory & motion study

Authors: Hartman SJ et al.

Summary: This randomised controlled trial in breast cancer survivors (mean age 57 years, 2.5 years post surgery) studied the effect of a 12-week physical activity programme (n = 43) versus control (n = 44), on objective and self-reported cognition. Oral Symbol Digit subscale scores (measure of processing speed) suggested differential improvement with exercise versus control (b = 2.01; p < 0.05), although between-group differences in self-reported cognition were not significant. Time since surgery altered the correlation; participants ≤2 years post-surgery had a greater improvement in Oral Symbol Digit score (exercise vs control b = 4.00; p < 0.01), but no improvement occurred in patients who were >2 years post-surgery (b = -1.19). A dose-response relationship occurred with greater increases in physical activity being associated with better self-reported and objective cognition.

Comment: "Chemo brain" is a commonly described phenomenon experienced by patients undergoing chemotherapy. There is increasing interest in research and potential interventions in this area. This study consisted of two arms, a control arm, and a physical activity intervention arm, which involved a 30-45 minute meeting with a clinical psychologist and/or a staff member trained by the clinical psychologist, to discuss and set physical activity goals of at least 150 minutes of moderate-to-vigorous activity per week, and utilisation of motivational interviewing techniques, provision of a Fitbit, and then emails and phone calls to provide further motivation during the 12 week intervention. Cognition was assessed using The National Institutes of Health Toolbox Cognition Domain at baseline and at 12 weeks, and self-reported cognition. Those who were enrolled within 2 years of diagnosis of breast cancer showed a significantly improved processing speed. These results are promising in terms of the benefit of exercise for these patients, and add yet another potential benefit of exercise for this group. Patients diagnosed with breast cancer therefore should be encouraged to undertake regular exercise, and linked with programs such as the Healthy Living after Cancer Program to assist with motivation.

Reference: Cancer 2018;124(1):192-202
Abstract

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials

Authors: Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Summary: This patient-level meta-analysis (n = 4756) examined the long-term benefits and risks of neoadjuvant chemotherapy (NACT; n = 2320) and the influence of tumour characteristics on outcome. Patients in 10 trials from 1983 to 2002 were included, median follow-up was 9 years and most chemotherapy was anthracycline based (81%). Overall, 69% of women receiving NACT had a complete or partial clinical response and the frequency of breast-conserving therapy was increased in NACT versus adjuvant chemotherapy (n = 1135) recipients (65% vs 49%). NACT had more frequent local recurrence than adjuvant chemotherapy, the 15-year local recurrence rate was 21.4% versus 15.9% (5.5% increase; 95% CI 2.4-8.6; RR 1.37; 95% CI 1.17-1.61; p = 0.0001). There was no difference for distant recurrence (15-year risk 38.2% vs 38.0%; RR 1.02; 95% CI 0.92-1.14), breast cancer mortality (34.4% vs 33.7%; RR 1.06; 95% CI 0.95-1.18), or all cause mortality (40.9% vs 41.2%; RR 1.04; 95% CI 0.94-1.15).

Comment: This meta-analysis has utilised patient-level data from 10 trials comparing neoadjuvant and adjuvant chemotherapy, undertaken prior to 2005. The study found that rates of breast-conserving surgery were higher for those given NACT, but that there was a higher risk of local recurrence for patients treated with NACT than for those treated with adjuvant chemotherapy. There was no difference however in distant recurrence rates, breast cancer mortality or overall mortality between the groups. In interpreting the data from this study, it is important to be aware that the management in most of these studies is substantially different to current management. None of the patients received trastuzumab in these studies and in only one of these trials did patients receive a taxane. Furthermore, in some of these studies those with a clinical response did not go on to receive any form of breast surgery. Also in some studies, neoadjuvant treatment was split with some given pre-operatively and some given post-operatively. Radiotherapy details have not been obtained, but may not have followed current standard management practices. When the trials in which not all patients had surgery post neoadjuvant chemotherapy were removed, the absolute increased risk of local recurrence was 3.2%, compared with 13.3% increased risk of local recurrence for those who received NACT with no surgery post chemotherapy. Data using current radiotherapy and chemotherapy regimens are required to determine whether there are differences in outcomes between patients managed with NACT and adjuvant chemotherapy with current management.

Reference: Lancet Oncol. 2018;19(1):27-39
Abstract

Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy

Authors: Denkert C et al.

Summary: This analysis of data from 6 randomised trials performed by the German Breast Cancer Group (n = 3771), examined the importance of tumour-infiltrating lymphocytes (TILs) for chemotherapy response and prognosis in patients with triple-negative (TN)/HER2-positive breast cancer, and luminal-HER2-negative breast cancer. A pathological complete response (pCR) was achieved by 45/759 (6%) patients with luminal-HER2-negative breast cancer with low TILs, 48/435 (11%) with intermediate TILs, and 49/172 (28%) with high TILs. In HER2-positive patients, pCR occurred in 194/605 (32%) patients with low TILs, 198/512 (39%) with intermediate TILs, and 127/262 (48%) with high TILs. In TN patients, pCR occurred in 80/260 (31%) patients with low TILs, 117/373 (31%) with intermediate TILs, and 136/273 (50%) with high TILs ($p < 0.0001$ for each subtype). In a univariate analysis, an increase of 10% in TILs prolonged disease-free survival in TN (HR 0.93; 95% CI 0.87-0.98; $p = 0{\cdot}011$) and HER2-positive (HR 0.94; 95% CI 0.89-0.99; $p = 0.017$), but not luminal-HER2-negative (HR 1.02; 95% CI 0.96-1.09) breast cancer. The TIL increase also prolonged OS in TN (HR 0.92; 95% CI 0.86-0.99; $p = 0.032$), but not HER2-positive (HR 0.94; 95% CI 0.86-1.02) breast cancer, and shortened OS in luminal-HER2-negative tumours (HR 1.10; 95% CI 1.02-1.19; $p = 0.011$).

Comment: The importance of the immune system in cancer, and the role of immunotherapy has been established for non-breast cancers, as well as increasing evidence for the role of immunotherapy in TN and HER2 positive breast cancer. TILs are an immunologic parameter, with higher levels of TILS on biopsies performed prior to commencement of neoadjuvant chemotherapy having been shown to be associated with response for both TN and HER2 positive breast cancer. This study investigated the association between TILs and various breast cancer outcomes for TN, HER2 positive and luminal-HER2-negative breast cancer, and found differing associations across these three groups for the measured outcomes. While higher levels of TILs on baseline biopsy were associated with higher pathologic complete response rates for luminal-HER2-negative, TN and HER2 positive breast cancer types, higher levels of TILs were only associated with improved disease free survival for those with HER2-positive and TN breast cancer, and improved OS only for TN breast cancer. Higher levels of TILs were associated with poorer OS for those with luminal-HER2-negative breast cancer. This study indicates further research is required into the differing associations across tumour subtypes, and suggests that there may need to be differing approaches to immunotherapeutic targets for different subtypes.

Reference: Lancet Oncol. 2018;19(1):40-50
Abstract

Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial

Authors: Colleoni M et al.

Summary: The multinational, open-label, randomised, parallel, phase III SOLE trial was conducted in 4851 postmenopausal women with hormone receptor-positive, lymph node-positive, and operable breast cancer who had completed 4-6 years of adjuvant endocrine therapy, to determine if extended intermittent adjuvant letrozole (2.5 mg/day for 9 months then a 3-month break for years 1-4; 2.5 mg/day for 12 months in year 5; n = 2425) was better than continuous letrozole (2.5 mg/day for 5 years; n = 2426) at improving breast cancer outcome. After a median 60-month follow-up, intermittent letrozole recipients had a disease-free survival rate of 85.8% (95% CI 84.2-87.2) versus 87.5% (95% CI 86.0-88.8) with continuous letrozole (HR 1.08; 95% CI 0.93-1.26). Adverse event rates did not differ between intermittent and continuous letrozole recipients; the most common grade 3-5 adverse events were hypertension (24% vs 21%) and arthralgia (6% vs 6%).

Comment: This study randomised patients who had already received between 4-6 years of endocrine therapy to a further 5 years of either continuous letrozole or intermittent use for 9 months followed by a 3-month break for years 1-4 and then daily for the 5th year. The study was designed to determine whether the intermittent schedule improved disease free survival. The disease free survival rate at a median of 60 months follow-up was high, and similar for both groups, at 85.8% in the intermittent group and 87.5% in the continuous group. It is important to note that almost half of the patients had received only aromatase inhibitor therapy previously, and evidence thus far has shown only very limited benefit in terms of extension of such continuous therapy beyond that time point. The lack of benefit of intermittent scheduling therefore may be because extension of aromatase inhibitor therapy in any form beyond 5 years is not beneficial. However, for those with previous SERM exposure, results appeared to favour the continuous arm, though this was not statistically significant. The results suggest that, for patients who have already undertaken 5 years of endocrine treatment, having breaks off treatment appears reasonably safe, and patients can be advised as such. Whether this data can be safely applied to the initial 5 years of therapy however, is unknown.

Reference: Lancet Oncol. 2018;19(1):127-38
Abstract

Phase II, multicentre, randomised trial of eribulin plus gemcitabine versus paclitaxel plus gemcitabine as first-line chemotherapy in patients with HER2-negative metastatic breast cancer

Authors: Park YH et al.

Summary: This multicentre, prospective, randomised, open-label, phase II study compared eribulin mesylate, a halichondrin non-taxane inhibitor of microtubule dynamics, plus gemcitabine (n = 59) with paclitaxel plus gemcitabine (n = 59) as first-line treatment in patients with HER2-negative metastatic breast cancer. The 6-month progression-free survival (PFS) rate (primary endpoint) did not differ between groups; 72% for eribulin plus gemcitabine and 73% for paclitaxel plus gemcitabine, nor did OS differ between the groups (not reached vs 21.2 months). Clinical benefit rates were 44% vs 49%. Major toxicities included neutropenia and neurotoxicity and neurotoxicity grade ≥II were more common with paclitaxel plus gemcitabine than with eribulin plus gemcitabine (13.6% vs 45.8%; $p < 0.0001$).

Comment: The combination of paclitaxel plus gemcitabine is increasingly used in practice for HER2-negative breast cancer, particularly for those with a greater burden of disease as a result of the high response rates and reasonably good side effect profile. However, peripheral neuropathy is a major dose-limiting toxicity experienced by patients undergoing this treatment regimen. This study investigated whether, as first-line therapy for metastatic HER2-negative breast cancer, eribulin plus gemcitabine was not inferior to paclitaxel plus gemcitabine and found similarly high 6-month PFS for both groups at 72% and 73%, respectively, but with lower neurotoxicity in the eribulin arm. Therefore for those patients for whom combination chemotherapy is indicated, eribulin plus gemcitabine is worth considering. However in the Australian context, such a combination would need to be utilised at a later line than first-line therapy due to PBS restrictions on eribulin use.

Reference: Eur J Cancer 2017;86:385-93
Abstract

The association between patient attitudes and values and the strength of consideration for contralateral prophylactic mastectomy in a population-based sample of breast cancer patients

Authors: Hawley ST et al.

Summary: This survey of newly diagnosed patients (n = 2578; response rate 71%) with early-stage breast cancer treated in 2013-2014 in Los Angeles or Georgia was conducted 7 months after surgery, to determine how individual decision styles and values are associated with the consideration of different treatment options including contralateral prophylactic mastectomy (CPM). Overall, 25% of women reported strong/very strong consideration of CPM, while 29% considered it moderately/weakly. The factors most valued at the time of treatment decision were: avoiding worry about recurrence (82%) and reducing the need for more surgery (73%). Multivariate analysis suggested that patients who preferred to make their own decisions, who valued avoiding worry about recurrence, or who valued avoiding radiation, more often strongly considered CPM ($p < 0.05$); those who reported being more logical or who valued keeping their breast did so less often.

Comment: Rates of contralateral prophylactic mastectomy have been shown to have increased for those without an increased risk of developing a second primary breast cancer to >20%, from a relatively low rate in US-based studies. This study examines consideration of prophylactic mastectomy by patients in Georgia and Los Angeles County between 2013 and 2014. Consideration was classified as weak, moderate, strong or very strong, or not at all. More than half the patients questioned considered CPM. The association between patients' values and decision styles and strong consideration of prophylactic mastectomy were examined, with strong consideration associated with certain decision styles and valuing reducing concern regarding recurrence and avoiding radiation. This study does not give follow-up information to advise which of these patients ultimately went on to receive CPM, which would be of interest. From a clinical perspective this data may assist in determining which patients are likely to wish to discuss CPM.

Reference: Cancer 2017;123(23):4547-55
Abstract

Impact of preexisting mental illness on all-cause and breast cancer-specific mortality in elderly patients with breast cancer

Authors: Iglay K et al.

Summary: The retrospective cohort study, conducted using US Surveillance, Epidemiology, and End Results (SEER)-Medicare data (2005-2007), compared all-cause and breast cancer-specific mortality in elderly (≥ 68 years of age) breast cancer (stage I to IIIa) patients (n = 19,028) with and without mental illness (3% had pre-existing severe mental illness). After adjustment for age, income, race, ethnicity, geographic location and marital status, there was a 2-fold increase in all-cause mortality hazard in those with versus those without severe mental illness (aHR 2.19; 95% CI 1.84-2.60). The breast cancer-specific mortality hazard was not significant (aHR 1.20; 95% CI 0.82-1.74).

Comment: This study investigated elderly patients with severe mental illness who were diagnosed with stage I to IIIa breast cancer between 2005 and 2007 and found that, compared to those without a mental illness, those with a mental illness had a significantly higher all-cause mortality hazard on adjusted analysis. The finding of higher likelihood of later diagnosis for those with mental health conditions highlights the importance of those involved in the care of these patients to ensure screening and/or examination is appropriately undertaken in this patient group. The finding of more aggressive tumour type in this patient group warrants further investigation into the determinants of this. Due to the nature of the design of this study, recurrence data has not been obtained. Such information would also be of interest.

Reference: J Clin Oncol. 2017;35(36):4012-18
Abstract

Long-term use of long-acting insulin analogs and breast cancer incidence in women with type 2 diabetes

Authors: Wu JW et al.

Summary: This population-based study using data from the United Kingdom's Clinical Practice Research Datalink (2002-2015) on 22,395 women with type 2 diabetes, assessed the long-term risk of breast cancer in patients receiving long-acting insulin analogs (glargine, detemir or neutral protamine Hagedorn [NPH] insulin). In total, 321 incident breast cancer events occurred during follow-up (incidence rate 3.3/1,000 person-years). Insulin glargine had an increased risk of breast cancer (HR 1.44; 95% CI 1.11-1.85) versus NPH insulin, predominantly increasing 5 years after glargine initiation (HR 2.23; 95% CI 1.32-3.77) and after >30 prescriptions (HR 2.29; 95% CI 1.26-4.16). The risk was higher in prior (HR 1.53; 95% CI 1.10-2.12) but not new insulin users. The risk associated with insulin detemir was not increased (HR 1.17; 95% CI 0.77-1.77).

Comment: Preclinical studies have found that long-acting insulin analogs, such as glargine, have stronger binding affinity to the insulin receptor family and there is concern that, as a result of this binding, breast cancer cell proliferation as well as inhibition of apoptosis of breast cancer cells, may occur. Furthermore exposure to insulin may increase the risk of cancerous transformation of breast epithelial cells. This UK-based study examined patients with at least one prescription for basal insulin (long-acting agents glargine or detemir, or the shorter acting NPH) during the defined study period, and examined the association with primary invasive breast cancer as the primary outcome. Confirming the concern from preclinical studies, there was a higher incidence of breast cancer in those who received glargine compared with NPH insulin (HR 1.44, 95% CI 1.11-1.85). No significant association was found with detemir and breast cancer; however, numbers using this agent were insufficient for conclusive analysis. Based on the data from this study, patients on long-acting insulin therapy may need to be advised of a potential increased risk of development of breast cancer. Further research is required to determine whether risk of recurrence is greater for patients on these agents following adjuvant treatment for breast cancer, or whether outcomes in the metastatic setting may be worse.

Reference: J Clin Oncol. 2017;35(32):3647-53
Abstract

Independent commentary by Dr Hilary Martin, who is a medical oncologist at Fiona Stanley Hospital Perth subspecialising in breast cancer. Her initial oncology training was undertaken in South Australia. She subsequently worked as a breast unit fellow at the Royal Marsden Hospital, London, and also as a clinical fellow at Royal Perth Hospital. She has a Masters of Public Health through the University of Sydney. Her research interests include mammographic breast density, survivorship, CTDNA, and lobular breast cancer.

