

**Original article****Menopausal symptom clusters and their correlates in women with and without a history of breast cancer: A pooled data analysis from the Women's Wellness Research Program**

*Short form title: Menopausal symptom clusters and breast cancer*

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**Funding**

Funding sources: Project Grant funding from the Cancer Council Queensland 2009 (to D.J.A.); Bluebox Proof of Concept Project Funding, QUT 2012 (to D.J.A.); NHMRC Partnership Grant 2013 (to D.J.A. and A.M.)

**Disclosure Statement**

No competing financial interests exist

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**Abstract**

**Objectives:** This analysis examined climacteric symptoms clusters in women with and without breast cancer, and explored how socio-demographic, health, and modifiable lifestyle factors predicted symptom clusters.

**Methods:** This pooled analysis of four Women's Wellness Research Program (WWRP) studies comprised individual level data from 969 Australian women aged 40-63 years, 293 of whom had been previously treated for breast cancer and 678 without a breast cancer history. Climacteric symptoms, menopausal status, socio-demographic characteristics, and health and lifestyle factors were assessed. Principal components analysis was used to determine symptoms clusters for each group separately before linear regression with backwards selection was used to identify the significant correlates of the identified clusters.

**Results:** Women with a history of breast cancer reported more sleep disturbance ( $P < 0.01$ ), difficulty concentrating ( $P < 0.01$ ), muscular/joint pain ( $P < 0.01$ ), crying ( $P < 0.01$ ) and irritability ( $P < 0.01$ ) and vasomotor symptoms ( $P < 0.01$ ) than women from the non-cancer group. Principal components analysis with quartimax rotation revealed two distinct solutions explaining 60.9% and 57.6% of the variance in the groups respectively. For both groups, symptom clusters were increased among those with unhealthy lifestyle behaviours (and chemotherapy among the after cancer group;  $P < 0.05$  for all) though to a lesser extent in the breast cancer group.

**Conclusions:** In this study, women after cancer reported a broad range of bothersome climacteric symptoms. Similar symptom clusters were also noted for women with and without a history of breast cancer, though correlates differed across groups, and might reflect different underlying aetiologies.

**Keywords:** Menopausal symptoms; Breast neoplasms; Symptom clusters; Modifiable lifestyle factors; Midlife; Pooled analysis.

Recent advances in medical technologies have significantly reduced breast cancer mortality and in many high income countries, 5-year survival is estimated to be between 85% and 90%<sup>1-5</sup>. Thus in many parts of the world, women previously treated for breast cancer (often known as breast cancer survivors) represent a growing proportion of the population who are often burdened with a number of chronic treatment-induced health effects. Some of the more common treatment-related effects include vasomotor symptoms<sup>6, 7</sup>, cognitive<sup>8</sup> and mood disturbances<sup>9</sup>, and sexual dysfunction<sup>10</sup>. These are attributed to the suppression of ovarian function arising from common antihormone and chemotherapy drugs. In younger women in particular, the sharp decline in endogenous estrogen associated with such treatments can cause premature menopause while for post-menopausal women, existing menopausal symptoms can be exacerbated<sup>11, 12</sup>. These symptoms are often more severe, sudden, frequent and endured for longer duration than the menopausal symptoms reported by women not treated for cancer<sup>12, 13</sup>.

While women after breast cancer generally report more intense classical (vasoactive) menopausal symptoms compared to women from the general population, less is known about the myriad of other symptoms that can occur at midlife, or whether they are interrelated. Population-based studies have shown complex interrelationships between multiple concurrent menopausal symptoms, though symptom clusters frequently differ across populations<sup>14</sup>. For example, among late reproductive American women cognitive/depressed mood/nervous tension grouped together and accounted for more than one-third of the total variance while hot flushes/night sweats/sleep disturbance/breast pain comprised a distinct second symptom cluster<sup>15</sup>. In contrast, another American study of women aged 45-60 grouped anxiety/irritability/fatigue with weight gain/incontinence and vaginal dryness/sleep disturbances<sup>16</sup>.

Less is known about menopausal symptom clusters in women after breast cancer treatment (though extensive work has broadly examined symptom clusters in women after

cancer, e.g., pain, fatigue, sleep disturbances, depression<sup>12, 17, 18</sup>). A population-based Scottish study showed that surgically-induced menopausal women reported the greatest frequency of classic menopausal symptoms (51% reporting at least one symptom and 14% all three symptoms)<sup>19</sup> and symptoms like vasomotor symptoms are frequently associated with decrements in quality of life<sup>16, 20</sup>. While in female breast cancer survivors specifically, 63% reported moderate-severe vasomotor symptoms (hot flushes, sleep problems, heart complaints), 63% reported moderate-severe psychological symptoms (depression, nervousness, impaired memory), and 37% reported moderate-severe somatic symptoms (sexual difficulties, urinary problems, vaginal dryness, joint and muscle problems)<sup>12</sup>.

Whether these symptoms form discrete menopausal symptom clusters in women after breast cancer is difficult to determine, and differences in symptom groupings might reflect different etiologies and pathophysiologies. Moreover, the presence or absence of certain modifiable lifestyle factors (e.g., body mass, exercise, alcohol intake, and tobacco smoking<sup>21-25</sup>) is associated with both the frequency and severity of menopausal symptoms though the extent to which these factors affect women after breast cancer is unclear.

The aims of this paper are two-fold: (1) To determine how individual midlife symptoms group together as clusters in women with and without a history of breast cancer, and; (2) to examine how these clustered symptoms are influenced by health and lifestyle factors in these two groups of women.

## **METHODS**

### **Participants and procedure**

This paper presents pooled data from the Women's Wellness Research Program (WWRP). The WWRP comprises a series of research projects that broadly aim to increase understanding of women's health and lifestyle behaviours and to develop effective

empirically-based interventions targeting a reduction of tobacco smoking, hazardous alcohol use, increasing water intake, improving diets and increasing physical activity. This analysis also includes individual-level baseline data from 969 Australian women from the Healthy Aging of Women Study (HOW)<sup>26-28</sup>; the Pink Women's Wellness Program<sup>29</sup>; the Bluebox Study<sup>30</sup>; and the Women's Wellness After Cancer Program (WWACP, trial ongoing). For the analysis, only women aged 40-63 years were included (this age range represents the expected age range at natural menopause  $\pm$  5 years). Women in the cancer-specific studies were excluded if they were missing a breast cancer diagnosis or if they had been diagnosed with other cancers, the treatment of which could result in ovarian suppression.

The study procedures and recruitment details have been outlined extensively in previous papers<sup>26-33</sup>. Briefly, the HOW is a longitudinal observational study of women randomly selected from the electoral roll that commenced in 2001. Women were recruited at random from rural and urban areas of southeast Queensland ( $n = 869$ ) and reinterviewed at 5-year intervals. Changes in measurement methods between 2001 and 2006 prevented baseline data from being included in this paper; therefore data from the second data collection point were used. The initial sample comprised 564 women aged 51-66, however, 84 women were excluded from this analysis (6% were missing breast cancer diagnosis or had been diagnosed with gynaecological cancer and 9% were older than 63 years).

All other studies included in this analysis were randomised controlled trials, designed to test the effectiveness of a 12-week structured wellness intervention on lifestyle modification (increased exercise, healthy eating, weight management, and reduced smoking and alcohol consumption) on reducing menopausal symptoms and health-related quality of life indices. The Pink Women's Wellness Program was designed for women after active treatment for breast cancer. The trial, which piloted a wellness intervention in 55 women aged 40-65, tested intervention efficacy in increasing quality of life and the uptake of healthy

lifestyle behaviours. Six participants in the Pink Women's Wellness Program were excluded from the present analysis on the basis of age, and one woman excluded because of other cancer diagnoses. The Bluebox Study was a proof-of-concept study for women at risk of, but not diagnosed with, chronic disease. The intervention was delivered to 225 Australian women aged between 40 and 65 years. Three different modes of the intervention were tested for effectiveness (again 2% were aged over 63 years and were not included in this analysis). The final study, the Women's Wellness after Cancer Program or WWACP, was designed for women who had previously received treatment for breast, gynaecological, and blood cancers (this study is ongoing). A total of 283 women, aged 34-72 years, provided the baseline data used in this analysis. Overall, 48 women outside of the defined age range or who did not provide their age were excluded from the present analysis, and 13 women not previously diagnosed with breast cancer (or had additional cancer diagnoses), were excluded from the analysis. Table 1 further outlines the procedure for deriving the final sample of 971 women included in this pooled analysis (see Table, Supplemental Digital Content 1, which details of the sample characteristics by study).

Insert table 1 about here

## **Measures**

Quantitative data were collected using a structured questionnaire.

### *Outcome variables*

The Greene Climacteric Scale© (GCS), was used to assess the climacteric symptoms often associated with midlife in all of the studies pooled for this analysis<sup>34</sup>. This instrument is a 21-item instrument validated in a variety of population-based and clinical samples<sup>34, 35</sup>. Each of the 21 items represents a specific symptom related to midlife (e.g., hot flashes, night sweats, sleep disturbance, dizziness, difficulty concentrating and sexual dysfunction).

Participants are asked to indicate the current severity of these symptoms on a four-point Likert scale: not at all (0), a little (1), quite a bit (2), extremely (3). Generally, symptoms are summed into four scales assessing self-reported vasomotor symptoms (items 19, 20), somatic symptoms (items 12-18), psychological symptoms (anxiety, items 1-6; depression, items 7-11), and sexual function (item 21)<sup>34</sup>. One goal of this paper is to explore the factor structure of the 21-item Greene Climacteric Scale in women with and without a history of breast cancer to symptom clusters in these two groups.

### *Predictor variables*

Several background socio-demographic factors and health behaviours are hypothesised to influence the frequency, intensity and temporal nature of menopausal symptoms. These include menopausal status, age, education, income, tobacco smoking, excess alcohol intake<sup>36</sup>, physical activity<sup>36</sup>, limited fruit and vegetable consumption<sup>36</sup>, and body mass index<sup>37</sup>. All of these variables were included in this analysis. In the majority of instances the pooled studies used comparable instruments to collect data, such as tobacco smoking, physical activity, and body mass index.

Overall, the instruments used to collect data on socio-demographic characteristics (according to the standards established by the Australian Bureau of Statistics [ABS]) were comparable, although in some instances variables were collapsed because of small cell sizes. Age was a continuous variable, while all others were categorical. Education was assessed by asking participants to indicate their highest level of education: “year 10 or less/junior school”, “year 12/senior school”, “technical certificate/diploma”, “university/college degree”. The detail in relation to gross household income varied between studies; hence the variable was collapsed to form the following ABS categories: less than \$20,000 AUD; \$20,001 - \$40,000 AUD; \$40,001 - \$60,000 AUD; \$60,001 - \$80,000 AUD; more than \$80,001 AUD; unsure.

Menopausal status was classified according to the Stages of Reproductive Aging Workshop (STRAW)<sup>38</sup> algorithm for menstrual cycle. Women were classified as premenopausal if they had a menstrual period in the past 3 months and there were no changes to the predictability of their menstrual cycle in the past 12 months; perimenopausal if they reported a menstrual period in the past 12 months but not in the past 3 months or if their menstrual cycle was less predictable in the past 12 months; postmenopausal if they had not had a period in the last 12 months; surgical if they reported having had a hysterectomy/oophorectomy, and; treatment-induced if they were pre-menopausal before cancer treatment but reported subsequent cessation of their menstrual periods and had received adjunct chemotherapy and/or antihormone drugs<sup>1</sup>.

All of the pooled studies used comparable instruments to collect self-report data on a range of health behaviours<sup>36</sup>. Smoking was assessed by examining current smoking status (non-smoker, past smoker, current smoker - regular, current smoker - causal); quantity (number of cigarettes per week); and frequency (years). Alcohol consumption examined the amount (number of standard drinks) and frequency (number of days where alcohol was consumed). Fruit and vegetable consumption was assessed using several indicators (see Table, Supplemental Digital Content 2, which details the items used to collect fruit and vegetable data and Figure, Supplemental Digital Content 3, which outlines the harmonisation procedure). This variable was collapsed to the frequency of consuming at least five portions of fruit and/or vegetables a day over an average week.

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<sup>1</sup> Though causality cannot be determined and menopausal transition might have occurred naturally during the 0-24 months between completing active treatment and participation in the study (as per the eligibility criteria), adjunct cancer therapies received at this time can exacerbate menopausal symptoms<sup>11-13</sup>.

Body mass index (BMI) was calculated from self-reported height and weight using the standard formula<sup>37</sup>. BMI scores < 18.5 kg/m<sup>2</sup> equal underweight, 18.5-24.9 kg/m<sup>2</sup> equal normal weight, 25.0-29.9 kg/m<sup>2</sup>, and scores ≥ 30 kg/m<sup>2</sup> are classified as obese. Physical activity was assessed in relation to the frequency of exercise in the past month<sup>36</sup>. Participants were asked to report the number of times they had exercised for at least 30 minutes at a time at a 'somewhat hard' exertion level. They were deemed to be sufficiently physically active if they responded "daily" or "5-6 times weekly".

Other covariates included past diagnosis with comorbid health conditions. For the purpose of this paper, comorbidities were defined as diabetes mellitus (excluding gestational diabetes), coronary heart disease (CHD), and stroke. Comorbidity occurrence was based on self-reported affirmative responses to questions interrogating if they had ever been diagnosed by a doctor or other health professional. For women previously diagnosed with breast cancer, several questions about treatment modalities and medications were also asked. For the purpose of this analysis, these variables were dichotomized (yes/no) to indicate whether women had received adjunct antihormone/chemotherapy drugs.

### **Data Harmonisation**

Generally, comparable measures were used across studies and therefore harmonisation was not required (for example, individual level socio-demographics, smoking status, and exercise). In instances where data harmonization was required, comparable measures were derived using individual level data (for example, alcohol use, fruit and vegetable consumption). Where variables were collected with varying detail or using different instruments, they were collapsed into their simplest form and data cleaning occurred throughout to check for missing values, implausible responses, and potential outliers. For an illustrative example see Table, Supplemental Digital Content 2, which details the items used

to collect fruit and vegetable data and Figure, Supplemental Digital Content 3, which outlines the harmonisation procedure.

### **Statistical analysis**

Data were pooled and analysed using the SPSS (Statistical Package for the Social Sciences) Version 23<sup>39</sup> statistical package. Descriptive statistics are expressed as counts, percentages and means (SD), while bivariate associations were analysed using  $\chi^2$  tests, t-tests, analysis of variance (ANOVA), or their non-parametric equivalent. Significance was set at  $\alpha = .05$ .

Principal components analysis (PCA) with quartimax rotation explored potential symptom clusters in women with and without a history of breast cancer. Preliminary analysis assessed the suitability of the data before PCA was performed as two separate analyses. Preliminary principal components analyses (PCA) used a direct oblimin rotation, but because factor correlations were less than 0.32, analyses were rerun using an orthogonal rotation<sup>40</sup>. Adequacy of the final factor (component) solutions for each analysis was determined if: (1) factor loadings  $\geq 0.4$ ; (2) a simple structure was obtained (i.e., high coefficients that loaded on one factor only); (3) Kaiser–Meyer–Olkin (KMO) value  $\geq 0.8$ ; and (4) significant Bartlett’s Test of Sphericity ( $p < 0.05$ ) was obtained<sup>41-43</sup>.

Multiple linear regression analyses were performed to assess the impact of menopausal status, socio-demographic characteristics (education, ethnicity), and lifestyle factors (BMI, smoking, alcohol, diet, exercise) on the weighted factors for each group (women with and without breast cancer). Models were adjusted for several potential confounders (e.g., age, study, and menopausal status) while all other variables were entered using a backward elimination method (Probability-of-F-to-remove  $\geq .100$ ). This approach was utilized to determine the relative impact of the variables on specific symptom clusters and to develop a parsimonious model of the correlates of menopausal symptom clusters in

these two groups<sup>16</sup>. Sensitivity analysis was then performed to determine the concordance of model results using stepwise linear regression.

## RESULTS

The pooled analysis showed some correlations between socio-demographic characteristics (for example, age, highest educational attainment, gross household income, and employment status,  $p < 0.01$ ), some health behaviours, and breast cancer diagnosis (see Table 2). For example, women previously treated for breast cancer were more likely to have exercised in the past month, but less frequently, compared to women without breast cancer ( $\chi^2 (3) = 16.57, p < 0.01$ ). Breast cancer survivors also reported less excess alcohol intake ( $\chi^2 (1) = 30.49, p < 0.01$ ) and were more likely to eat at least 5 serves of fruit and vegetables daily ( $\chi^2 (1) = 213.93, p < 0.01$ ).

Insert table 2 about here

Table 3 presents the severity of climacteric symptoms (GCS items) by breast cancer history. In many instances, women previously treated for breast cancer reported more climacteric symptoms and in greater severity. This was particularly evident with regard to sensory somatic and vasomotor symptoms. 64.3% of women after breast cancer reported tingling or numbness and 36.4% reported loss of sensation in hands/feet compared with a lesser proportion of women without breast cancer (32.5% and 19.1% respectively,  $p < 0.01$  for both). Moreover, 82.2% of breast cancer survivors reported being bothered by hot flushes (40.4% quite a bit and 15.0% extremely) compared to 39.1% of women without breast cancer (8.2% quite a bit and 3.9% extremely). Similar patterns were noted for night sweats and decreased sexual interest (Table 3).

Insert table 3 about here

Two separate analyses (PCA) examined climacteric symptoms clusters in women with and without breast cancer history. In both instances the final factor solutions yielded KMOs  $\geq$  0.8 and significant Bartlett's tests (KMO = 0.81,  $p < 0.01$  and KMO = 0.89,  $p < 0.01$  for women with and without breast cancer respectively) and provided the most simple structure. Results of the PCAs are detailed in table 4.

Insert table 4 about here

*Factor analysis of symptoms in women previously treated for breast cancer*

A six-factor solution accounted for 60.9% of the variance characterised by prior breast cancer treatment. Factor 1 explained 17.6% of the variance and included mainly psychological symptoms such as feeling tense or nervous, attacks of panic, difficulty concentrating, tiredness or lack of energy, loss of interest, feeling unhappy or depressed, crying spells, and irritability. Factor 2 included classic vasoactive symptoms such as hot flushes, night sweats, and low libido and explained 11.0% of the variance. Factor 3 included sensory somatic symptoms: dizziness/feeling faint, pressure or tightness in head or body, headaches, and sleep disturbance (9.8% of the variance explained). Factor 4 explained 9.2% of the variance and included peripheral somatic/pain symptoms like difficulty concentrating, numbness or tingling, muscle/joint pains, and loss of sensation in hands/feet. Symptoms of nervous tension (Factor 5) accounted for 7.3% of the total variance and included rapid heartbeat, excitable, and panic attacks, while the final factor (Factor 6) included two somatic symptoms (rapid heartbeat and breathing difficulties) and explained 5.7% of the variance.

*Factor analysis of symptoms in women without breast cancer history*

PCA derived a five-factor solution for women not previously diagnosed with breast cancer, which accounted for 57.6% of the variance in this group. The predominant factor explained the majority (25.5%) of this variance. This factor included feeling tense or nervous, difficulty sleeping, panic attacks, difficulty concentrating, tiredness or lacking in energy, loss of interest in most things, feeling unhappy or depressed, crying spells, irritability, and headaches (psychological symptoms). Factor 2 included vasoactive symptoms, such as hot flushes and night sweats. Factor 3 included peripheral somatic/pain symptoms like numbness or tingling, muscle/joint pains, and loss of sensation in hands/feet (accounting for 9.0% and 8.9% of variance respectively). Factor 4 included sensory somatic symptoms: dizziness/feeling faint, pressure or tightness in head or body, and breathing difficulties. The final factor (Factor 5) included symptoms of nervous tension (rapid heartbeat, nervous tension, panic, and excitability) and accounted for 6.3% of the total variance.

*Comparability of factor loadings across groups*

The specific menopausal symptoms associated with each symptom cluster are summarized in Table 5. Five symptom clusters were found to be similar (though not identical) in women with and without a history of breast cancer. Cluster names were derived from the constellation of symptoms, i.e., psychological symptom cluster, vasoactive symptom cluster, sensory somatic symptom cluster, peripheral somatic symptom cluster, and nervous tension symptom cluster. Among the after cancer group, three symptoms cross-loaded (i.e., feeling tense or nervous, difficulty in concentrating, heart beating quickly) while in the non-breast cancer group, one symptom cross-loaded (i.e., headaches). Also of note, was that one factor did not load in women without cancer (i.e., loss of sexual interest) while two symptoms (i.e., rapid heartbeat and breathing difficulties) formed a distinct factor seen only in women after cancer (Factor 6 is not shown in Table 5).

Insert table 5 about here

### *Linear regression*

All models were adjusted for age, menopausal status and discrete study within the program before other variables were entered into the linear regression, using the backwards selection method.

Insert table 6 about here

For women previously treated for breast cancer, socio-demographic characteristics, modifiable lifestyle factors and cancer treatments explained only 1% of the variance in psychological symptoms and yielded no significant correlations while vasoactive symptoms were correlated with age ( $B = -0.03$ ,  $SE = 0.15$ ,  $p = 0.03$ ) only. Decrements in sensory somatic symptoms (Factor 3) were correlated with regular physical activity (exercising 3-4 times weekly,  $B = -0.52$ ,  $SE = 0.16$ ,  $p < 0.01$ ; exercising 5 or more times weekly,  $B = -0.48$ ,  $SE = 0.20$ ,  $p = 0.02$ ). Menopausal status (post-menopause,  $B = 1.21$ ,  $SE = 0.49$ ,  $p = 0.01$ ; and treatment-induced menopause,  $B = 1.31$ ,  $SE = 0.46$ ,  $p < 0.01$ ) was associated with increments in Factor 3. Peripheral somatic symptoms were higher among women who reported comorbidities ( $B = 0.80$ ,  $SE = 0.26$ ,  $p < 0.01$ ) and who had received chemotherapy ( $B = 0.77$ ,  $SE = 0.16$ ,  $p < 0.01$ ), and lower among women who were employed outside of the home ( $B = -0.51$ ,  $SE = 0.18$ ,  $p < 0.01$ ). Factor 5 (nervous tension) was positively correlated with body mass index ( $B = 0.04$ ,  $SE = 0.01$ ,  $p < 0.01$ ), peri-menopause ( $B = 1.05$ ,  $SE = 0.48$ ,  $p < 0.01$ ) and treatment-induced menopausal symptoms ( $B = 1.00$ ,  $SE = 0.47$ ,  $p = 0.04$ ). Finally, general somatic symptoms (Factor 6), a factor which were unique to women after breast

cancer, removed all predictor variables during the backward elimination process, retaining only age, menopausal status, and study (none of which were significant).

Among women without a previous breast cancer diagnosis, the predictors of menopausal symptoms differed somewhat. Increments in psychological symptoms (Factor 1) were associated with inadequate fruit and vegetable consumption ( $B = 0.30$ ,  $SE = 0.08$ ,  $p < 0.01$ ), past ( $B = 0.19$ ,  $SE = 0.07$ ,  $p < 0.01$ ) and current ( $B = 0.34$ ,  $SE = 0.16$ ,  $p = 0.03$ ) cigarette smoking. Age ( $B = -0.03$ ,  $SE = 0.01$ ,  $p < 0.01$ ) and frequent physical activity (exercise 3-4 times weekly,  $B = -0.30$ ,  $SE = 0.09$ ,  $p < 0.01$ ; exercise 5 or more times weekly,  $B = -0.39$ ,  $SE = 0.09$ ,  $p < 0.01$ ) were associated with decrements in psychological symptoms. Vasoactive symptoms were positively correlated with menopausal status (peri-menopausal,  $B = 0.90$ ,  $SE = 0.19$ ,  $p < 0.01$ ; post-menopausal,  $B = 1.15$ ,  $SE = 0.19$ ,  $p < 0.01$ ; surgical menopause,  $B = 1.77$ ,  $SE = 0.19$ ,  $p < 0.01$ ) and being married or in a de facto relationship ( $B = 0.22$ ,  $SE = 0.09$ ,  $p = 0.01$ ).

Peripheral somatic symptoms (Factor 3) showed positive associations with menopausal status (peri-menopausal,  $B = 0.54$ ,  $SE = 0.19$ ,  $p < 0.01$ ; post-menopausal,  $B = 0.75$ ,  $SE = 0.19$ ,  $p < 0.01$ ; surgical menopause,  $B = 1.08$ ,  $SE = 0.19$ ,  $p < 0.01$ ), and comorbidities ( $B = 0.58$ ,  $SE = 0.15$ ,  $p < 0.01$ ) and a negative association with employment ( $B = -0.24$ ,  $SE = 0.08$ ,  $p < 0.01$ ). Sensory somatic symptoms were only significantly correlated with ethnicity (Australia/New Zealand,  $B = -0.32$ ,  $SE = 0.09$ ,  $p < 0.01$ ) and body mass index ( $B = 0.02$ ,  $SE = 0.01$ ,  $p < 0.01$ ), while symptoms of nervous tension (Factor 5) were decreased in those who exercised regularly (3-4 times weekly,  $B = -0.33$ ,  $SE = 0.10$ ,  $p < 0.01$ ; 5 or more times weekly,  $B = -0.31$ ,  $SE = 0.10$ ,  $p < 0.01$ ) and who were employed ( $B = -0.16$ ,  $SE = 0.08$ ,  $p = 0.04$ ).

Sensitivity analysis examined the concordance of model results using stepwise linear regression. Outputs are outlined in Supplemental Digital Content 4. This analysis largely

supported model findings with two exceptions; in women without breast cancer, employment was not significantly correlated with peripheral somatic symptoms or nervous tension. Also of note, though coefficients and standard errors for age did not change between analyses, in women after breast cancer it was no longer a significant predictor of vasoactive symptoms.

## DISCUSSION

This pooled analysis provided a valuable opportunity to examine the severity and clustering of menopausal symptoms in two groups of women; those with and with breast cancer. We found differences not only in the frequency and severity of climacteric symptoms between groups, but also in the symptoms clusters and their correlates.

Many previous studies in women after breast cancer have focussed on vasomotor symptoms (VMS). In this group symptoms are often more severe, and can be attributed to treatment-induced oestrogen deficiency. In this study, we found that women treated for breast cancer reported not only more severe VMS, but also a myriad of other climacteric symptoms, when compared to women without breast cancer. More specifically, many of the breast cancer survivors in this sample commonly reported frequent sleep disturbance (82.1%), fatigue (91.0 %), difficulty concentrating (75.2%), and muscular/joint pain (84.1%). These results are in stark contrast to Conde and colleagues who found similar prevalence of menopausal symptoms in women with and without breast cancer<sup>44</sup>.

Menopausal symptom clusters showed some notable similarities across groups. Though not identical, a core set of symptoms was identified (i.e., psychological/depressive symptoms that comprised nervousness/tension, panic, difficulty concentrating, fatigue, loss of interest, feeling unhappy/depressed, and crying spells) and these were consistent with previous work<sup>16, 45</sup>. Nevertheless, despite the generally similar structures across five of the six symptom clusters, it is possible that the underlying symptoms are attributable to different

causes (i.e., cancer treatment or not). For example, Factor 6 was unique to women after cancer (rapid heartbeat and breathing difficulties). Rapid heartbeat (or tachycardia) is reported in more than one-third of women receiving anticancer therapy and might reflect treatment-induced cardiac injury<sup>46</sup>. It is equally plausible, however, that these symptoms could be attributed to anaemia (a common complication of cancer treatment that impairs oxygen delivery<sup>47</sup>), stress and anxiety, weight gain, or loss of cardiorespiratory fitness, all of which are commonly reported among cancer therapies<sup>48</sup>.

Psychological symptom clusters accounted for the majority of variance in both groups and regression models examined the predictors of these clusters. Among women after cancer, no significant correlations were noted and the proposed model only explained around 1.0% of the variance in this factor. Previous studies of psychological symptoms in breast cancer survivors have been mixed. Some studies have suggested that 'pre-cancer' factors like socio-economic, health, and lifestyle factors are probable risk factors for depressive symptoms<sup>49, 50</sup>, while others have found that these symptoms are possibly treatment-induced<sup>51, 52</sup>. In this study, we examined both 'pre-cancer' and treatment-related factors but failed to identify any potential predictors. In contrast, for women without breast cancer, psychological symptoms were associated with a number of lifestyle behaviours including past and present smoking, inadequate fruit and vegetable intake, and physical activity. There is a plethora of research outlining the benefits of exercise and other healthy lifestyle behaviours on mental health<sup>53-55</sup> and our results seem to echo these findings but generally only among the non-cancer group.

Among women without breast cancer, decreased libido did not form part of the menopausal symptom clusters having failed to achieve a significant factor loadings ( $\geq 0.4$ ). In contrast, among the after cancer group decreased libido clustered with vasomotor symptoms. The presence of this cluster suggests that for women in this group, symptoms are largely endocrinal, though the inherent complexity of sexual dysfunction means that these symptoms

also need to be considered within the context of broader psychosocial factors. For example, while some cancer treatments can cause changes in endocrine patterns, leading to low oestrogen circulating and contributing to atrophic vaginitis<sup>56</sup>, concurrent changes in body image are also likely to play a significant role in sexual function. Moreover, vasomotor symptoms (VMS), which are often severe in women after cancer, are linked to altered cortical arousal and disrupted sleep architecture<sup>57, 58</sup> which might adversely affect sexual desire and arousal. It is possible that the difference in the clustering of VMS in women with and without a history of breast cancer might represent different aetiological mechanisms, although further research is needed to confirm this hypothesis.

Notably for women after breast cancer, some menopausal symptom clusters like peripheral somatic symptoms and nervous tension can be plausibly explained in relation to the cancer experience rather than menopausal transition. In this group, peripheral somatic symptoms, pain, and difficulty concentrating formed one cluster (Factor 4). The concurrence of these symptoms might reflect past chemotherapy treatment, because chemotherapy-induced peripheral neuropathy (CIPN)<sup>59</sup> and decreased cognitive function or ‘chemobrain’<sup>60</sup> are common side-effects of some chemotherapeutic agents. Moreover, the symptoms of nervous tension (panic, tension, rapid heartbeat, excitability) could reflect a fear of cancer recurrence (FCR) which is commonly reported in women after breast cancer<sup>61</sup>.

Several study limitations should be noted. Many of the women who contributed to this analysis were derived from convenience samples, and were enrolled in wellness trials. This might have skewed the sample towards women who are dissatisfied with aspects of their health and lifestyle and motivated to change them. Also, menopausal symptoms are commonly thought to differ by ethnicity, yet this sample was largely homogenous (82% were born in Australia/New Zealand), and variations attributable to ethnicity might have been minimised. Finally, sensitive analysis revealed discordant results for employment and Factors

3 (peripheral somatic) and 5 (nervous tension) in women without cancer and also for age and Factor 2 (vasoactive) in women after cancer. These differences might be explained in relation to low statistical power though further research is needed to confirm or refute study findings.

## **CONCLUSION**

Despite these limitations, we were able to explore the severity and concurrence of menopausal symptoms in two groups of midlife women (i.e., those with and without a history of breast cancer). For women after cancer, multiple bothersome climacteric symptoms including, but not limited to VMS, were common. While similar structures were noted in five of the six menopausal symptom clusters, their correlates differed. It is possible that despite these similarities, clusters might reflect distinct pathophysiologies and etiologies, though further research is needed. An improved understanding of the nature and concurrence of treatment-related menopausal symptoms is needed to improve management protocols.

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**Table 1.** Characteristics of the pooled studies included in the Women's Wellness Research Program (WWRP, n = 1,127)

Study	Year of baseline survey	Number of follow-up time points	Participants at baseline (n)	Response Rate <sup>a</sup>	Excluded by age <sup>c</sup>	Excluded by cancer diagnosis <sup>b</sup>	Participant contributing data to the analysis <sup>d</sup>
HOW	2006 <sup>e</sup>	3	564	64%	9%	6%	480
Pink	2013	1	55	81%	12%	1%	48
Bluebox	2013	1	225	90%	2%	0	221
WWACP	2015	2	283	-	17%	5%	222

HOW, Health Aging of Women study; Pink, Pink Women's Wellness Program (Breast Cancer); Bluebox, Bluebox Proof of Concept study; WWACP, Women's Wellness after Cancer Program (Breast and Gynaecological Cancer).

<sup>a</sup> Reflects response rate from time 1 to time 2

<sup>b</sup> Women were excluded if data were missing for breast cancer diagnosis, secondary cancer diagnoses, or among WWACP women who reported gynaecological/haematological cancer but not breast cancer

<sup>c</sup> Women aged <40 and ≥ 64 were excluded (age range at natural menopause 45-58 years ± 5 years)

<sup>d</sup> Overall number might vary because of missing data

<sup>e</sup> Time 2 questionnaires was used as baseline questionnaire (completed in 2001) provided limited data on variables of interest

**Table 2.** Characteristics of women by history of breast cancer diagnosis

Variables	Breast cancer group (n = 293) <sup>a</sup>	Non breast cancer group (n = 678) <sup>a</sup>
	M (SD) or % (n)	M (SD) or % (n)
Age M (SD)	52.1 (6.8)**	56.1 (5.4)
Employment status % (n)		
Employed	82.1 (239)**	60.9 (412)
Home duties	10.0 (29)	18.2 (123)
Retired	4.5 (13)	15.8 (107)
Other	3.4 (10)	5.2 (35)
Gross household income % (n)		
Less than \$20,000	1.4 (5)**	3.6 (24)
\$20,001 - \$40,000	4.2 (13)	10.1 (68)
\$40,001 - \$60,000	9.0 (29)	23.4 (158)
\$60,001 - \$80,000	15.6 (41)	16.5 (111)
more than \$80,001	56.6 (186)	45.0 (303)
unsure	13.2 (38)	1.5 (10)
Country of birth % (n)		
Australia/New Zealand	75.8 (219)**	84.4 (578)
Europe	17.3 (50)	12.0 (82)
Elsewhere	6.9 (20)	3.6 (25)
Marital status % (n)		
Married or de facto	77.9 (225)	79.7 (538)
Separated/divorced/widowed	12.5 (36)	13.8 (93)
Single (never married)	9.7 (28)	6.5 (44)
Highest educational attainment % (n)		
Year 10 or less	10.7 (31)**	35.4 (239)
Year 12	11.8 (34)	12.1 (82)
Technical certificate or diploma	22.1 (64)	17.5 (119)
University degree or higher	55.4 (160)	35.0 (242)
Menopausal status % (n)		
Pre-menopausal	2.1 (6)**	5.9 (40)
Peri-menopausal	14.8 (43)	11.7 (79)
Post-menopausal	40.5 (118)	78.5 (532)
Surgical/treatment induced	42.6 (124)	4.0 (27)
Inadequate fruit and vegetable consumption % (n) <sup>b</sup>	32.8 (96)**	81.1 (548)
Excess alcohol intake <sup>c</sup>	8.9 (26)**	24.2 (164)
Body Mass Index		
Normal (<25 kg/m <sup>2</sup> )	36.1 (101)	35.3 (234)
Overweight (25-29.9 kg/m <sup>2</sup> )	36.4 (102)	33.9 (225)
Obese (≥30 kg/m <sup>2</sup> )	27.5 (77)	30.8 (204)
Exercise in the past month % (n)		
None	33.7 (98)**	24.6 (166)
1-2 times weekly	32.6 (95)	28.7 (194)
3-4 times weekly	19.2 (56)	23.5 (159)

5 + times weekly	14.4 (42)	23.2 (157)
Smoking status % (n)		
never	65.0 (1843)	60.9 (406)
past	30.7 (87)	33.9 (226)
current	4.3 (12)	5.2 (35)

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\*  $p < 0.05$       \*\*  $p > 0.01$

<sup>a</sup> overall n's might differ because of missing data

<sup>b</sup> Consumes less than 5 serves of fruit and vegetables daily

<sup>c</sup> Consumed alcohol on  $\geq 6$  nights and/or  $\geq 5$  standard drinks were sitting in the past week

**Table 3.** Climacteric symptoms in women with and without a history of breast cancer <sup>a</sup>

	Breast cancer group (n = 293)				Non breast cancer group (n = 678)				p
	Not at all % (n)	A little % (n)	Quite a bit % (n)	Extremely % (n)	Not at all % (n)	A little % (n)	Quite a bit % (n)	Extremely % (n)	
Heart beating quickly or strongly	68.1 (196)	25.0 (72)	5.6 (16)	1.4 (4)	69.4 (465)	26.3 (176)	4.2 (28)	0.1 (1)	.07
Feeling tense or nervous	33.6 (97)	51.6 (149)	13.1 (38)	1.7 (5)	41.5 (279)	43.8 (295)	13.2 (89)	1.5 (10)	.12
Difficulty in sleeping	17.9 (52)	43.8 (127)	27.2 (79)	11.0 (32)	29.4 (198)	41.3 (278)	22.9 (154)	6.4 (43)	<.01
Excitable	72.0 (206)	23.1 (66)	4.9 (14)	0	64.4 (429)	28.7 (191)	6.5 (43)	0.5 (3)	.10
Attacks of panic	71.5 (206)	23.6 (69)	4.1 (12)	0.3 (1)	75.1 (502)	20.1 (134)	3.9 (26)	0.9 (6)	.44
Difficulty in concentrating	24.8 (72)	51.0 (148)	19.3 (56)	4.8 (14)	42.9 (289)	45.5 (307)	10.5 (71)	1.0 (7)	<.01
Feeling tired or lacking in energy	9.0 (26)	43.1 (124)	36.8 (106)	11.1 (32)	14.9 (100)	49.6 (332)	26.8 (179)	8.7 (58)	<.01
Loss of interest in most things	54.9 (158)	36.5 (105)	6.6 (19)	2.1 (6)	62.9 (423)	27.1 (182)	7.6 (51)	2.4 (16)	.04
Feeling unhappy or depressed	45.3 (130)	45.3 (130)	7.7 (22)	1.7 (5)	52.7 (353)	36.6 (245)	9.1 (61)	1.6 (11)	.087
Crying spells	63.3 (183)	30.4 (88)	4.5 (13)	1.7 (5)	78.5 (527)	17.1 (115)	3.6 (24)	0.7 (5)	<.01
Irritability	33.0 (95)	51.0 (147)	14.9 (43)	1.0 (3)	41.3 (276)	44.6 (298)	11.5 (77)	2.5 (17)	.02
Feeling dizzy or faint	72.8 (209)	22.3 (64)	4.2 (12)	0.7 (2)	74.1 (498)	22.2 (149)	2.7 (18)	1.0 (7)	.62
Pressure or tightness in head/body	65.9 (189)	26.1 (75)	6.6 (19)	1.4 (4)	75.4 (507)	19.5 (131)	3.9 (26)	1.2 (8)	.02
Parts of body feel numb/tingling	35.7 (102)	45.8 (131)	13.6 (39)	4.9 (14)	67.5 (449)	25.9 (172)	5.0 (33)	1.7 (11)	<.01
Headaches	56.3 (160)	35.6 (101)	7.0 (20)	1.1 (3)	52.0 (349)	38.5 (258)	7.6 (51)	1.9 (13)	.54
Muscle and joint pains	15.9 (46)	39.4 (114)	32.5 (94)	12.1 (35)	23.7 (159)	51.0 (342)	18.9 (127)	6.4 (43)	<.01
Loss of feeling hands or feet	63.6 (182)	23.8 (68)	8.7 (25)	3.8 (11)	80.9 (539)	14.4 (96)	3.5 (23)	1.2 (8)	<.01
Breathing difficulties	76.7 (220)	19.9 (57)	2.4 (7)	1.0 (3)	82.7 (554)	13.9 (93)	2.5 (17)	0.9 (6)	.14
Hot Flushes	17.8 (51)	26.8 (77)	40.4 (116)	15.0 (43)	60.9 (408)	27.0 (181)	8.2 (55)	3.9 (26)	<.01
Sweating at night	30.8 (88)	31.8 (91)	27.3 (78)	10.1 (29)	62.4 (419)	26.4 (177)	8.0 (54)	3.1 (21)	<.001
Loss of interest in sex	20.5 (58)	35.7 (101)	25.8 (73)	18.0 (51)	25.6 (169)	32.9 (217)	25.5 (168)	15.9 (105)	.368

<sup>a</sup> n's might differ because of missing data

**Table 4.** Factor loadings for women with and without a history of breast cancer using principal components analysis with quartimax rotation

Symptoms	Women after breast cancer						Women without breast cancer				
	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
Heart beating quickly/strongly					0.470	0.518					0.556
Feeling tense or nervous	0.487				0.540		0.710				
Difficulty in sleeping			0.422				0.481				
Excitable					0.574						0.655
Attacks of panic	0.422				0.625		0.524				0.456
Difficulty in concentrating	0.423			0.417			0.656				
Feeling tired/lacking energy	0.504						0.741				
Loss of interest in most things	0.810						0.766				
Feeling unhappy or depressed	0.849						0.835				
Crying spells	0.684						0.590				
Irritability	0.679						0.745				
Feeling dizzy or faint			0.682								0.556
Pressure/tightness in head/body			0.718								0.705
Parts of body feel numb/tingling				0.776					0.739		
Headaches			0.703				0.544				0.442
Muscle and joint pains				0.464					0.659		
Loss of feeling hands or feet				0.862					0.791		
Breathing difficulties						0.684					0.501
Hot Flushes		0.857						0.853			
Sweating at night		0.878						0.856			
Loss of interest in sex		0.520									
Variance explained (%)	17.6	11.0	9.8	9.2	7.3	5.7	25.5	9.0	8.9	7.8	6.3

**Table 5.** Comparability of factor loadings for women with and without a history of breast cancer

Symptoms	Psychological symptoms <sup>a</sup>		Vasoactive symptoms <sup>b</sup>		Sensory somatic symptoms <sup>c</sup>		Peripheral somatic symptoms <sup>d</sup>		Symptoms of nervous tension <sup>e</sup>	
	BCG	NBCG	BCG	NBCG	BCG	NBCG	BCG	NBCG	BCG	NBCG
Heart beating quickly or strongly									X	X
Feeling tense or nervous	X	X							X	
Difficulty in sleeping		X			X					
Excitable									X	X
Attacks of panic	X	X							X	X
Difficulty in concentrating	X	X					X			
Feeling tired or lacking in energy	X	X								
Loss of interest in most things	X	X								
Feeling unhappy or depressed	X	X								
Crying spells	X	X								
Irritability	X	X								
Feeling dizzy or faint					X	X				
Pressure or tightness in head or body					X	X				
Parts of body feel numb or tingling							X	X		
Headaches		X			X	X				
Muscle and joint pains							X	X		
Loss of feeling hands or feet							X	X		
Breathing difficulties						X				
Hot Flashes			X	X						
Sweating at night			X	X						
Loss of interest in sex			X							

BCG, Breast cancer group; NBCG, Non breast cancer group

<sup>a</sup> Psychological symptoms represent Factor 1 for both groups

<sup>b</sup> Vasoactive symptoms represent Factor 2 for both groups

<sup>c</sup> Sensory somatic symptoms represent Factor 3 BCG and Factor 4 NBCG

<sup>d</sup> Peripheral somatic symptoms represent Factor 4 BCG and Factor 3 NBCG

<sup>e</sup> Symptoms of nervous tension represents Factor 5 for both groups

**Table 6.** Linear regression models of climacteric symptoms in women with and without a history of breast cancer using backward elimination <sup>a</sup>

Variables	Breast cancer group (n = 293)						Non breast cancer group (n = 678)					
	Psychol- ogical <i>B (SE)</i>	Vasoactive <i>B (SE)</i>	Sensory somatic <i>B (SE)</i>	Peripheral somatic <i>B (SE)</i>	Nervous tension <i>B (SE)</i>	General somatic <i>B (SE)</i>	Psychol- ogical <i>B (SE)</i>	Vasoactive <i>B (SE)</i>	Peripheral somatic <i>B (SE)</i>	Sensory somatic <i>B (SE)</i>	Nervous tension <i>B (SE)</i>	
<i>Socio-demographics</i>												
Age	-0.01 (0.01)	-0.03 (0.01)*	-0.02 (0.01)	0.03 (0.01)*	-0.02 (0.02)	-0.02 (0.01)	-0.03 (0.01)**	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	
Ethnicity												
ANZ										-0.32 (0.09)**		
Europe			0.36 (0.18)									
Married or de facto							0.22 (0.09)*					
Employed (Full/part-time)				-0.51 (0.18)**					-0.24 (0.08)**		-0.16 (0.08)*	
<i>Modifiable lifestyle factors</i>												
Current smoker							0.34 (0.16)*					
Past smoker		0.27 (0.14)	0.24 (0.14)				0.19 (0.07)**					
BMI					0.04 (0.01)**					0.02 (0.01)**		
Exercise in the past month												
1-2 times weekly							-0.15 (0.08)				-0.17 (0.09)	
3-4 times weekly			-0.52 (0.16)**	-0.26 (0.16)			-0.28 (0.09)**				-0.33 (0.10)**	
5 + times weekly			-0.48 (0.20)*				-0.39 (0.09)**		-0.16 (0.09)		-0.31 (0.10)**	
Excess alcohol <sup>b</sup>	0.43 (0.25)	0.46 (0.24)						0.16 (0.09)				

Inadequate diet <sup>c</sup>							0.30 (0.08)**		0.15 (0.09)		
<i>Menopausal status</i>											
Peri-menopause	-0.13 (0.48)	0.34 (0.46)	0.92 (0.48)	0.11 (0.47)	1.05 (0.48)*	-0.62 (0.49)	-0.03 (0.16)	0.90 (0.19)**	0.54 (0.19)**	0.01 (0.17)	0.26 (0.17)
Post-menopause	0.06 (0.48)	0.93 (0.46)	1.21 (0.49)*	-0.14 (0.48)	0.95 (0.50)	-0.12 (0.49)	0.14 (0.17)	1.15 (0.19)**	0.75 (0.19)**	-0.17 (0.18)	0.09 (0.18)
Surgical or treatment-induced	-0.33 (0.46)	0.85 (0.44)	1.31 (0.47)**	0.10 (0.46)	1.00 (0.47)*	-0.39 (0.47)	-0.13 (0.16)	1.77 (0.19)**	1.08 (0.19)**	0.08 (0.17)	0.17 (0.17)
<i>Comorbidities <sup>d</sup></i>				0.80 (0.26)**					0.58 (0.15)**		
<i>Cancer treatments <sup>e</sup></i>											
Chemotherapy			0.31 (0.16)	0.77 (0.16)**	0.38 (0.17)*						
Adjusted <i>R</i> <sup>2</sup>	0.011	0.097	0.089	0.148	0.061	0.006	0.121	0.138	0.084	0.030	0.019

*B (SE)* represents the unstandardized coefficient and standard error for the variables retained in the final model after backwards selection and adjustment for age, study, and menopausal status; ANZ, Australian or New Zealander; BMI, body mass index.

\*  $p < 0.05$       \*\*  $p > 0.01$

<sup>a</sup> All models adjusted for age, menopausal status, and study

<sup>b</sup> Consumed alcohol on  $\geq 6$  nights and/or  $\geq 5$  standard drinks were sitting in the past week

<sup>c</sup> Consumes less than 5 serves of fruit and vegetables daily

<sup>d</sup> Comorbidities were defined as CHD, stroke, diabetes

<sup>e</sup> Cancer treatments included in the analysis were radiation, chemotherapy, and other treatments

**Supplemental Digital Content**

Supplemental Digital Content 1. Table that details of the sample characteristics by study. pdf

Supplemental Digital Content 2. Table that details the items used to collect fruit and vegetable data. pdf

Supplemental Digital Content 3. Figure that outlines the harmonisation procedure. pdf

Supplemental Digital Content 4. Table that provides results of the sensitivity analysis of climacteric symptoms. pdf