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The preventable burden of breast cancers for premenopausal and postmenopausal women in Australia: a pooled cohort study

Running title: Preventable breast cancer burden in Australia

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KEYWORDS

Breast cancer, risk factors, population attributable fraction, preventable burden, cohort

ABBREVIATIONS

45&Up	45 and Up Study
AICR	American Institute of Cancer Research
ALSWH	Australian Longitudinal Study on Women's Health
AusDiab	Australian Diabetes, Obesity and Lifestyle Study
BMES	Blue Mountains Eye Study
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
ICD-O	International Classification of Diseases for Oncology

LADY	Learning how Australians Deal with menopause sYmptoms Survey
MCCS	Melbourne Collaborative Cohort Study
MET	Metabolic Equivalent of Task
MHT	Menopausal hormone therapy
NHS	National Health Survey
NWAHS	North West Adelaide Health Study
OC	Oral contraceptive
PAF	Population attributable fraction
PR	Prevalence
WCRF	World Cancer Research Fund

NOVELTY AND IMPACT

This is the first study to show regular alcohol consumption as the leading modifiable cause of breast cancer burden for premenopausal women (12.6%). Using the latest exposure prevalence information, we rank body fatness as the leading cause of preventable breast cancer burden for postmenopausal women (12.8%) in Australia, with regular alcohol consumption also contributing substantially (6.6%). We identify several sub-populations with the highest preventable postmenopausal breast cancer burden and the most to gain from interventions.

ABSTRACT

Estimates of the future breast cancer burden preventable through modifications to current behaviours are lacking. We assessed the effect of individual and joint behaviour modifications on breast cancer burden for premenopausal and postmenopausal Australian women, and whether effects differed between population subgroups. We linked pooled data from six Australian cohort studies (N=214,536) to national cancer and death registries, and estimated the strength of the associations between behaviours causally related to cancer incidence and death using adjusted proportional hazards models. We estimated exposure prevalence from representative health surveys. We combined these estimates to calculate Population Attributable Fractions (PAFs) with 95% confidence intervals (CIs), and compared PAFs for population subgroups. During the first 10-years follow-up, there were 640 incident breast cancers for premenopausal women, 2,632 for postmenopausal women, and 8,761 deaths from any cause. Of future breast cancers for premenopausal women, any regular alcohol consumption explains 12.6% (CI=4.3-20.2%), current use of oral contraceptives for ≥5 years 7.1% (CI=0.3-13.5%), and these factors combined 18.8% (CI=9.1-27.4%). Of future breast cancers for postmenopausal women, overweight or obesity (BMI ≥25 kg/m^2) explains 12.8% (CI=7.8-17.5%), current use of menopausal hormone therapy (MHT) 6.9% (CI=4.8-8.9%), any regular alcohol consumption 6.6% (CI=1.5-11.4%), and these factors combined 24.2% (CI=17.6-30.3%). The MHT-related postmenopausal breast cancer burden varied by body fatness, alcohol consumption and socio-economic status, the body fatness-related postmenopausal breast cancer burden by alcohol consumption and educational attainment, and the alcohol-related postmenopausal breast cancer burden by breast feeding history. Our results provide evidence to support targeted and population-level cancer control activities.

KEYWORDS breast cancer, risk factors, population attributable fraction, preventable, cohort

INTRODUCTION

Breast cancer is the most common cancer in women worldwide[1] and the second leading cause of cancer death in Australian women.[2] Several potentially modifiable hormonal and behavioural risk factors have been identified.[1,3-5]

For breast cancer for premenopausal women, there is convincing evidence, according to the criteria for grading evidence of carcinogenicity by expert review panels,[1,4] that use of combined oestrogen-progestogen oral contraceptives (OCs) increases the risk, with this excess risk decreasing with increasing time since last use.[3,4] There is also probable evidence that alcohol consumption increases, and vigorous physical activity, body fatness, and breastfeeding, decreases the risk.[1] There is suggestive evidence that any type of physical activity and consuming foods containing carotenoids, dairy products or diets high in calcium may decrease the risk.[1]

For breast cancer for postmenopausal women, there is convincing evidence that current use of oestrogen-progestogen menopausal hormone therapy (MHT) increases the risk, with this excess risk increasing with increasing duration of use, and decreasing after stopping treatment.[3,4] Alcohol consumption, body fatness and adult weight gain are also established risk factors for postmenopausal breast cancer, while there is probable evidence that physical activity, body fatness in young adulthood and breastfeeding decrease the risk.[1,5] There is suggestive evidence that consuming foods containing carotenoids or diets high in calcium may decrease the risk.[1]

The burden of breast cancer preventable by modifications to certain causally-related risk factors can be quantified by calculating population attributable fractions (PAFs). Only one cohort study has

evaluated the individual and joint contributions of modifiable risk factors on the breast cancer burden for premenopausal women,[6] and several[6-26] have examined the breast cancer burden for postmenopausal women. All previous studies evaluated the complete removal of the exposure, even though a gradual reduction in exposure might be more realistic. And, although change in exposure distribution may affect both cancer incidence and death, no study accounted for potential competing risk of death, which can bias PAF estimates.[27] Moreover, no study has assessed whether the burden of breast cancer differs between population subgroups, information which could inform targeted prevention activities.

To address these gaps we applied a comprehensive PAF method to a large, prospective pooled Australian cohort and contemporaneous prevalence data, and quantified the future burden of breast cancer for premenopausal and postmenopausal women preventable by modifications to behaviours, in the overall population and population subgroups.[27,28]

METHODS

Cohort data

We used individual-level data from the Australian cancer-PAF cohort consortium,[28] which comprises seven well-established Australian prospective cohort studies, six of which included women: Melbourne Collaborative Cohort Study (MCCS), Blue Mountains Eye Study (BMES), Australian Longitudinal Study on Women's Health (ALSWH), Australian Diabetes, Obesity and Lifestyle Study (AusDiab), North West Adelaide Health Study (NWAHS), and the 45 and Up Study (45&Up). The final study sample comprised 207,505 women after excluding 1,959 who enrolled in

more than one cohort, 1,820 who did not consent to record linkage, and 7,031 with a history of breast cancer.

The Australian Institute of Health and Welfare Ethics Committee approved the study (EC2013/4/62).

Menopausal status definition

We applied the following algorithm to classify women's menopausal status at baseline: women who reported menstruating regularly, having had a menstrual period in the last 12 months or not having gone through menopause (premenopausal); women who reported currently going through menopause or having irregular menstrual periods (perimenopausal); and women who reported having gone through menopause or stopping menstruation, naturally or after bilateral oophorectomy (postmenopausal).[29] Menopausal status can be masked by hysterectomy or MHT use. We applied an age-based classification[29] for such women: < 45 years and with hysterectomy (premenopausal); ≥ 55 years and with hysterectomy or taking MHT (postmenopausal); and 45-54 years with hysterectomy or taking MHT (menopausal status unknown). These categories correspond to the age at which 90% of women with known menopausal status in our cohort had not reached (< 45 years), or had reached (55 years), menopause. We also classified women with missing menstruation or menopause data on the basis of these age categories. We then evaluated incident breast cancers in premenopausal and postmenopausal women identified on the basis of the above hiearchical definition. Breast cancers in women with perimenopausal or unknown menopausal status were not evaluated.

Prevalence data

We obtained risk factor exposure prevalence estimates from the national population-based AusDiab Study (1999-2000),[30] the LADY (Learning how Australians Deal with menopause sYmptoms) Survey (2013),[31] sampled to be representative for use of MHT, and the Australian National Health Surveys (NHS 2014-2015 and 2001)[32,33] (**Table 1, Supplementary Table 1**). The AusDiab Study and LADY Survey had information on menopausal status, and were therefore used as the primary data sources for generating exposure prevalences for premenopausal and postmenopausal women, respectively. Where information on a particular exposure was not available from these data sources, the most recent NHS was used, with menopausal status defined by the age criteria above (i.e. physical activity for postmenopausal women from NHS 2014-2015 and breastfeeding for premenopausal women from NHS 2001; **Supplementary Table 1**).

Data collection and harmonisation

We examined potentially modifiable hormonal and behavioural exposures with convincing, probable or suggestive evidence of a causal association with premenopausal or postmenopausal breast cancer, as judged by expert review panels[1,3-5] if they were measured in our cohort and available sources of prevalence data. These exposures were OC use, alcohol consumption, physical activity, breastfeeding, body fatness (body mass index (BMI)) and MHT use, ascertained at baseline. For MHT and OC use, we also examined duration of use and time since stopping use, but we did not have information on composition. We harmonised the exposures across the cohort studies and external prevalence data sources **(Supplementary Table 1**), both as continuous variables and classifying them in accordance with current evidence on dose-response relationships[1,3-5] or current Australian recommendations for healthy living for the cancer burden

analyses.[28] The current Australian recommendations are to not drink more than two standard alcoholic drinks per day, to do at least 150 min of moderate or 75 min of vigorous physical activity per week, to breastfeed exclusively for around six months and continue breastfeeding until 12 months if possible, to maintain a healthy weight (BMI $\leq$ 25 kg/m^2) and to limit MHT use to the shortest duration possible. However, as there is evidence for any regular alcohol consumption increasing the risk of breast cancer,[1] we used a more relevant categorisation in our analyses (0 drinks/day, < 1 drink/day, 1-2 drinks/day, > 2 drinks/day). Similarly, as there is evidence for thebreast cancer risk increasing with increasing duration of current MHT use[3,4] or OC use,[34,35] we categorised the current use by duration as available in our data (i.e. < 1 year, 1-4 years, 5-9 years, $\geq$ 10 years of current MHT use; and < 5 years or $\geq$ 5 years of current OC use).

We also harmonised non-modifiable exposures associated with breast cancer risk available in our data:[1] age, height, nulliparity and personal history of ovarian cancer, available in all or most cohorts, as well as first-degree family history of breast or ovarian cancer, personal history of breast cancer screening (recommended 2-yearly for women aged 50-74 years in Australia), age at menarche, age at first birth and age at menopause, collected in one to three cohorts, to allow adjustment for potential confounders (**Supplementary Table 1**). We further harmonised country of birth, marital status, educational attainment, socio-economic status and residential location (rurality) for subgroup analyses.

Data linkage and ascertainment of outcomes

We probabilistically linked the pooled cohort to the Australian Cancer Database and National Death Index to identify cancers and deaths. These records were available until 31st December 2012, providing 8-22 years follow-up (**Table 1**).

We classified primary invasive breast cancers of epithelial origin according to the International Classification of Diseases for Oncology (ICD-O-3; C50). Classification of tumours according to expression of hormonal receptors (i.e. oestrogen receptor, progesterone receptor and epidermal growth factor receptor) was not possible as these data were not collected by the Australian Cancer Database.

Statistical methods

We performed separate analyses for premenopausal and postmenopausal women. We defined follow-up as the time from baseline to the date of breast cancer diagnosis, death or end of follow-up, whichever occurred first. We estimated the strength of association between the risk factors and breast cancer and death using a parametric piecewise constant exponential hazards model, and expressed them as hazard ratios (HR) and their 95% confidence intervals (CI). We included the first 10-years of follow-up to generate comparable estimates across the cohorts, and evaluated and tested heterogeneity between cohorts using the asymptotic DerSimonian and Laird Q statistic and a complementary I^2 statistic.[36]

For both premenopausal and postmenopausal women we first modelled each breast cancer risk factor separately, adjusted for age and study. We then modelled all risk factors together, and retained factors significantly associated with breast cancer in the final model. We computed the

corresponding exposure prevalence (PR) estimates from the health surveys, and combined them with the strength of association estimates to calculate PAFs and their 95% CIs for the individual and joint contribution of the modifiable exposures to the breast cancer burden (Appendix 1).[27,37] Our PAF method accounts for potential competing risk of death and risk factor interdependence, and allows a flexible choice of the risk and reference level for the hypothetical exposure modification. We evaluated scenarios in which the exposure was either completely removed or reduced. We tested for potential differences in the distribution of the preventable breast cancer burden by other exposures and socio-demographic factors, by including an interaction term between the risk factor and the potential effect modifying factor in the model and calculating the 95% confidence interval for the difference in PAF estimates between the categories of the effect modifying factor.[37,38] If this confidence interval did not include zero, the PAF estimates were deemed to differ.

We conducted sensitivity analyses adjusting for potential confounding factors only available for different subsets of participants and excluding the first year of follow-up, to assess the potential effect of reverse causality. Additionally, some women who are premenopausal at baseline may go through menopause and become postmenopausal during follow-up, and thus have their breast cancer diagnosed in a perimenopausal or postmenopausal state. We, therefore, conducted further sensitivity analyses for premenopausal women: i) limiting their follow-up to five years and ii) censoring them at 55 and 50 years of age. Finally, we compared the PAF estimates obtained from the pooled cohort data to those obtained by meta-analysing the cohort-specific PAF estimates, weighting them by the inverse of their variance.

We estimated the number of breast cancers for premenopausal and postmenopausal women in Australia over the next 10 years that could be attributed to the current behavioural and hormonal risk factors by multiplying the PAF estimates by the projected numbers of breast cancers during 2017-2026 using a published method and data.[39]

We used SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and our publicly available PAF program.[38]

RESULTS

The median age at baseline was 46 years (interquartile range 22-48) for premenopausal women and 63 years (interquartile range 57-71) for postmenopausal women. We observed 640 incident breast cancers for premenopausal women, 2,632 incident breast cancers for postmenopausal women, and 8,761 deaths from any cause, during the first 10 years follow-up (**Table 1**). Premenopausal women were followed-up for 389,772 person-years, or a median of 10 (interquartile range 4.9-10.0) years per person, and postmenopausal women for 793,703 person-years, or a median of 4.7 (interquartile range 4.3-6.9) years per person.

Non-modifiable risk factors

We found no significant heterogeneity between the cohort-specific HRs for breast cancer for premenopausal or postmenopausal women in relation to non-modifiable risk factors (**Supplementary Tables 2 and 3**).

Older age at baseline and at first birth were associated with a higher risk of breast cancer for premenopausal women (**Supplementary Table 4**). Older age at baseline, greater height, nulliparity,

family history of breast cancer, older age at first birth and late menopause (after age 55) were associated with a higher risk of breast cancer for postmenopausal women (**Supplementary Table 4**).

Modifiable risk factors

We identified no significant between cohort heterogeneity for breast cancer for premenopausal or postmenopausal women in relation to modifiable behavioural or hormonal risk factors (**Supplementary Tables 5 and 6**).

In the multivariable adjusted model, breast cancer risk for premenopausal women was positively associated with *any regular* (> 0 drinks/day) alcohol consumption (P for trend = 0.001) and current OC use for five or more years (P for trend = 0.02) (**Table 2**), and was not associated with body fatness, physical activity or breastfeeding (**Supplementary Table 7**). The strength of these associations did not change materially after excluding the first year of follow-up, limiting the follow-up to five years, or censoring at age 55 or 50 years in sensitivity analyses (data not shown).

Breast cancer risk for postmenopausal women was positively associated with overweight or obesity (BMI $\geq$ 25 kg/m^2) (P for trend < 0.001) with risk especially elevated for BMI $\geq$ 35 kg/m^2, consumption of at least 1 alcoholic drink a day (P for trend = 0.002), and current MHT use for at least one year (P for trend < 0.001) (**Table 3**). Vigorous physical activity was associated with breast cancer risk (HR 0.97; 95% CI, 0.94-0.999 per hour/week increase) but moderate physical activity and physical activity according to the Australian recommendations were not (**Supplementary Table 7**). Neither was breastfeeding (**Supplementary Table 7**). The strength of these associations

was also unchanged after adjustment for family history of breast cancer, personal history of breast cancer screening, or age at menopause, or after excluding the first year of follow-up in sensitivity analyses (data not shown).

Competing risk of death

No exposure, other than age among postmenopausal women, was associated with a greater risk of death than of breast cancer (**Supplementary Table 8**).

Risk factor exposure prevalence

Regular alcohol consumption was highly prevalent among premenopausal (48%) and postmenopausal (58%) women (**Tables 2 and 3**). Of premenopausal women, 27% currently used OCs, the great majority (81%) for five or more years. Of postmenopausal women, 58% were overweight or obese, and 14% currently used MHT, most (79%) for five or more years. Sixty-two percent of premenopausal women had at least one of the two risk factors and 87% of postmenopausal women at least one of the three risk factors (**Supplementary Tables 9 and 10**).

Preventable breast cancer burden

Overall, 12.6% of the future burden of breast cancer for premenopausal women is attributable to any regular alcohol consumption, and 7.1% to current OC use for five or more years (**Table 2**). These PAFs correspond to up to 2,600 and 1,400 breast cancers respectively over the next 10 years. Jointly, these two factors are responsible for 18.8%, or 3,800 breast cancers for premenopausal women over that time. We observed no effect modification of the breast cancer burden for

premenopausal women attributable to its risk factors by other exposures or socio-demographic factors (data not shown).

The largest potentially modifiable future breast cancer burden for postmenopausal women is attributable to overweight or obesity (12.8%), followed by current MHT use (6.9%) and any regular alcohol consumption (6.6%) (**Table 3**). This translates to up to 17,500, 9,400, and 9,000 breast cancers in the next 10 years, respectively. The burden attributable to these three factors combined is 24.2% or 33,000 breast cancers for postmenopausal women. The burden attributable to alcohol consumption is mostly explained by an average of at least one alcoholic drink a day (4.4%), and the burden attributable to current MHT by use for 5 years or more (6.4%). Exposures to these two factors at these levels, together with overweight or obesity, explain up to 22.1% (30,200 breast cancers). Using MHT for 1-4 years instead of five years or longer could potentially avoid 4.0% and having a BMI 25-34.9 kg/m^2 instead of $\geq$ 35 kg/m^2 2.1% of the breast cancer burden for postmenopausal women.

No notable differences were observed when these PAF estimates obtained from the pooled cohort data were compared to the meta-analysed cohort-specific PAF estimates (**Supplementary Table 11**).

The burden of breast cancer for postmenopausal women attributable to its risk factors appears to be modified by other exposures and socio-demographic factors (**Table 4**). The burden attributable to current MHT use is higher for healthy weight compared with overweight or obese women (10.4% compared with 4.5%, P-difference = 0.01), for those consuming at least one alcoholic drink a day

compared with non-regular drinkers (11.1% compared with 3.8%, P-difference = 0.004), and for women of high compared with low socio-economic status (9.6% versus 3.1%, P-difference = 0.04). These findings are not explained by differences in duration of MHT use (data not shown). The postmenopausal breast cancer burden attributable to body fatness is higher for women currently drinking no or less than one alcoholic beverage a day compared with current regular drinkers (15.6% and 20.7% compared with 2.1% respectively, P-difference = 0.02 and 0.003 respectively), for women with low or intermediate compared with high educational attainment (20.2% and 15.0% compared with -8.5% respectively, P-difference <0.001 and 0.002 respectively), and for women 65 years or older at baseline compared to younger women (18.3% compared with 7.9%, P-difference = 0.03). The alcohol-related burden is higher for women who had ever breastfed compared with non-breast feeders (12.1% compared with -9.6%, P-difference = 0.001).

DISCUSSION

We find that regular alcohol consumption is the potentially modifiable risk factor responsible for the largest burden of breast cancer for premenopausal women in Australia, accounting for 12.6% of the burden and 2,600 cases of breast cancer over the next 10 years. Body fatness is responsible for the largest preventable burden of breast cancer for postmenopausal women (12.8% and 17,500 breast cancer cases over 10 years), with alcohol consumption also contributing substantially (6.6% and 9,000 breast cancer cases). We confirm that use of OCs by premenopausal women and of MHT by postmenopausal women significantly increase the burden of breast cancer in these groups (7% or 1,400 cases, and 7% or 9,400 cases, respectively). Jointly, these behavioural and hormonal factors explain about one fifth of the breast cancer burden, amounting to 36,800 cases of breast cancer over

the next 10 years in Australia. We also identified variation in the preventable burden of breast cancer for postmenopausal women by other exposures and sociodemographic factors.

Although the increased risk of breast cancer for premenopausal women associated with any regular alcohol consumption[1,40] and increased duration of current OC use[34,35] has been reported previously, this is the first study to quantify the excess burden of breast cancer for premenopausal women attributable to any regular alcohol consumption (12.6%), current OC use for five or more years (7.1%) and these two factors combined (18.8%). Our results did not support an association of low body fatness, physical inactivity and non-breastfeeding with breast cancer for premenopausal women.[1] The single previous French cohort study (497 cases) reporting PAF estimates for breast cancer for premenopausal women did not observe increased burden in relation to any behavioural or hormonal factors,[6] but those consuming less than one alcoholic drink a day were included in the reference category, and duration of OC use was not accounted for.

Our finding of a trend in breast cancer risk with increasing alcohol consumption, consistent with the worldwide evidence,[1] suggests that reducing numbers of drinks per day, among drinkers, would likely reduce breast cancer risk. However, we did not find significant reductions in burden with hypothetical changes from more than 2 daily drinks to 1-2 or less than 1 drinks per day. Our findings highlight that neither the current Australian recommendation for females to not drink more than two alcoholic drinks a day, nor the WCRF/AICR recommendation to not drink more than one drink a day, will eliminate the breast cancer burden attributable to alcohol.

Any recommendation regarding the use of OCs must take into consideration their risks and benefits. OCs increase the risk of breast cancer in young women, as well as the risk of liver and cervical cancers, but protect against endometrial, ovarian and colorectal cancers, and also provide reproductive health benefits.[4] In Australia and internationally, it is not current public health policy to recommend that women restrict their use of OCs; the latest position statement from Cancer Council Australia concludes that over the course of a woman's lifetime the net effect of OCs is cancer protective (the transient increased risk of breast and cervical cancer is outweighed by the reduced lifetime risk of endometrial and ovarian cancer).[41]

In Australia, three in five postmenopausal women are currently overweight or obese,[32] which we estimate to contribute 12.8% of the future breast cancer burden for postmenopausal women. A prior Australian study reported that 7.8% of the breast cancer burden for postmenopausal women in 2010 was attributable to body fatness, prevalent in two in five postmenopausal women in 2001.[15] These findings indicate an increasing body fatness–related breast cancer burden for postmenopausal women.

We estimate that 6.6% of the future breast cancer burden for postmenopausal women is attributable to any current regular alcohol consumption, and 4.4% attributable to the consumption of an average of one or more alcoholic drinks a day. Two prior PAF studies[24,25] attributed 5.9%-6.6% of breast cancer burden for postmenopausal women to any regular alcohol consumption but did not report the exposure prevalence used. Two other studies[6,16] attributed 5.6%-7.0% of the burden to consuming one or more alcoholic drinks a day, on the basis of a higher exposure prevalence (39%-43%) and including those consuming less than one drink a day in the reference category. None of the reported

estimates were statistically different from each other or from our estimates, showing that the alcohol-attributable burden appears relatively similar across eras and countries, in keeping with the relatively stable prevalence of alcohol consumption.[42]

We attributed 6.9% of the future breast cancer burden for postmenopausal women to any current MHT use. Comparison with previous PAF estimates (3.2%-27%)[6,9,13,14,19,23,24] from different eras and countries is not meaningful because of (i) variation in the prevalence estimates, due to decline in MHT use following the publication of the Women's Health Initiative trial and other results around 2002[29,31,43]; and (ii) variation in the hazard ratios, due to differences in the distribution of MHT composition and duration, with oestrogen-progestogen MHT increasing breast cancer risk to a greater extent than oestrogen-only MHT[4,29]. We show for the first time that most of the MHT-related future breast cancer burden is attributable to five or more years duration of use (6.4% out of 6.9%), with 4.0% of the burden avoidable by limiting use to less than five years; this is largely a consequence of a substantial proportion (79%) of MHT users being long term users. Our data show that MHT use for 1-4 years also increases breast cancer risk, but four in five current MHT users in Australia use MHT for at least 5 years.[31] Our findings thus support the current Australian and international recommendations of using MHT for the shortest duration possible, and only to alleviate menopausal symptoms, not for the prevention of chronic disease.[44,45]

Neither physical activity according to the Australian recommendations (at least 150 minutes of moderate or 75 minutes of vigorous activity per week, i.e. around 15 MET-hours) nor breastfeeding, two probable protective factors, were associated with breast cancer risk and burden for postmenopausal women in our study. This was consistent with two large cohort studies.[6,24] A prior

Australian study used strength of association estimates from the WCRF/AICR and attributed 8% of breast cancers for postmenopausal women in 2010 to not doing at least 300 minutes of moderate activity per week (around 30 MET-hours).[18] Significant associations between physical activity and breast cancer risk and burden have been observed when comparing very low and very high levels of physical activity,[16,25] however the transition from the first to the latter is not a very realistic target for cancer prevention. The WCRF/AICR found a weak protective association between breastfeeding and overall breast cancer risk, but not risk of breast cancers for premenopausal and postmenopausal women separately.[1]

We estimate that body fatness, regular alcohol consumption and any current MHT use jointly explain 24.2% of the future breast cancer burden for postmenopausal women in Australia. This is the first PAF estimate for the joint effects of these three established causal behavioural and hormonal factors for this cancer.

No prior study has evaluated differences in preventable breast cancer burden between population subgroups. In line with previous evidence of effect modification of the breast cancer risk for postmenopausal women,[46,47] we found effect modification of the burden attributable to MHT use by body fatness and alcohol use. Postmenopausal women experienced MHT-related burden at all body fatness and alcohol consumption levels, but those with a healthy weight and those consuming one or more alcoholic drinks a day had a higher MHT-related burden. We also found other novel differences between population subgroups. If confirmed, these findings are likely to contribute important evidence for individual and population-level cancer control strategies.

Strengths and limitations

The key strengths of our study include access to large individual-level prospective cohort data and population-based contemporary exposure prevalence data. This allowed us to harmonise exposure data across sources according to evidence-based categories or public health recommendations. We also harmonised data on menopausal status using established conventions,[29] while most prior studies used simple varying age categories to distinguish premenopausal and postmenopausal women. Applying an advanced PAF methodology to these data allowed us to estimate and compare the effect of both individual and joint behaviour modifications on the future breast cancer burdens, accounting for the first time for their interdependence and competing risk of death, even though the latter was not strong.

We examined all modifiable exposures with convincing or probable evidence of causality, except for adult weight gain and postmenopausal breast cancer[1]. Weight gain prior to menopause has been found to contribute more to the breast cancer burden for postmenopausal women than weight gain since menopause[12], with only the latter modifiable in currently postmenopausal women. Of the modifiable exposures with suggestive evidence of causality,[1] we could only examine physical activity in relation to breast cancer risk for premenopausal women. None of the dietary factors with suggestive evidence of an association with breast cancer for premenopausal or postmenopausal women were available from both the cohort and prevalence data sources. For alcohol consumption, our reference category of non-regular drinkers included former drinkers, who likely have a higher risk than never drinkers[48] which would understimate the association between current alcohol consumption and breast cancer risk, and result in conservative PAF estimates. We did not have information on the composition of either OC or MHT use, and thus our results describe the average

avoidable burden with the current exposure distribution. We also did not have information on the method of hormonal contraception, i.e. whether OC, hormonal IUD, injection or implant, but as different methods of hormonal contraception have been associated with an increased breast cancer risk,[34] this unlikely affects our conclusions. The duration of OC or MHT use was measured at baseline but the overall duration including follow-up is likely to be longer. Other exposures measured at baseline, as well as menopausal status, may also have changed during follow-up, but there is a latency period between exposure and cancer diagnosis and transition into menopause can take years.

Although the maximum follow-up time in our study was 10 years, the median follow-up time among postmenopausal women was only 5 years, which may have attenuated some of the associations. Furthermore, although the latest available prevalence estimates for both alcohol consumption and OC use date back to 1999-2000, the prevalence of alcohol consumption in Australian women (8% consumed > 2 drinks/day in 2001 and 9% in 2014-2015)[28] and the prevalence of hormonal contraception in other similar developed countries[49] appears to have remained stable since then.[28,49] Finally, the uncertainty in the exposure prevalence estimates should be incorporated in future PAF estimates, as per the uncertainty in the strength of the exposure-cancer association estimates.

Sensitivity analyses did not indicate reverse causality, confounding by non-modifiable factors available in one or two cohorts, or potential premenopausal status misclassification influencing the exposure-cancer associations. The possibility of residual confounding due to factors not collected by the cohorts, such as birth weight, family history of breast cancer in 2nd degree relatives, age at

diagnosis of 1st or 2nd degree relatives with breast cancer, previous breast biopsy or history of atypical breast cancer, or factors not yet identified as causal, cannot be excluded. Despite the large data sample, our power was limited for some analyses, including for specific exposure categories and those assessing potential effect modification of the breast cancer burden for premenopausal women. Finally, PAF estimation assumes immediate risk reduction following the hypothetical behavior modification, while with actual behavior modification there is a lag in risk and burden reduction. After stopping MHT and OC use, the lag is estimated to be no more than five years[29,50], while more evidence on the lag time following weight loss and reduction in alcohol consumption is needed to better inform future burden estimates.

Conclusion

Tackling obesity and overweight, regular alcohol consumption, and use of MHT are all likely to substantively reduce breast cancer cases in Australia; they are estimated to cause 17,500, 11,600 and 9,400 breast cancer cases over the next 10 years, respectively, given the latest available prevalence estimates. Premenopausal women who regularly drink alcohol and postmenopausal women with excess weight bear the greatest future burden of respective preventable breast cancers in Australia. We also identified subpopulations of postmenopausal women experiencing higher burden attributable to the these risk factors which, if confirmed, might derive even higher benefit from targeted preventive strategies.

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DECLARATION OF INTERESTS

Prof Canfell is a co-PI of an unrelated investigator-initiated trial of cytology and primary HPV screening in Australia ("Compass"), which is conducted and funded by the Victorian Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However, neither Prof Canfell or her institution on her behalf (Cancer Council NSW) receives direct funding from industry for this trial or any other project.

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Table 1. Characteristics of the individual and pooled cohort and external data sources

Characteristic	Cohort data						
	MCCS	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**45&Up**	**Pooled**
Baseline year(s)	1990-1994	1992-1993	1996	1999-2000	1999-2003	2006-2009	1990-2009
State/Territory	VIC	NSW	All	All	SA	NSW	All
Pre-menopausal women							
Population (n)	7,666	77	21,052	2,518	854	15,016	47,183
Incident breast cancer cases (n)[4]	181	2	186	30	7	234	640
Deaths (n)[4]	72	3	145	24	12	64	320
Age in years at baseline, median (interquartile range)	45 (42-48)	51 (50-53)	22[5] (20-46)	38 (33-43)	36 (29-40)	48 (47-50)	46 (22-48)
Post-menopausal women							
Population (n)	14,615	1,891	13,419	2,592	778	103,074	136,369
Incident breast cancer cases (n)[4]	414	49	407	78	25	1659	2,632
Deaths (n)[4]	683	308	2,327	329	92	4,702	8,441
Age in years at baseline, median (interquartile range)	61 (56-65)	67 (60-74)	72 (70-73)[5]	64 (57-71)	66 (60-73)	63 (57-71)	63 (57-71)

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and L
LADY (Learning how Australians Deal with menopause sYmptoms) survey; MCCS (Melbourne Collaborative Cohort Study); NHS (N
NWAHS (North West Adelaide Health Study); SA (South Australia); VIC (Victoria)

[1] The AusDiab study was used as the primary source to generate exposure prevalences for premenopausal women. The study population are no exclusions

[2] The LADY study was used as the primary source to generate exposure prevalences for postmenopausal women

[3] Menopausal status based on age criteria only, i.e. women aged ≥ 55 years are considered postmenopausal and women aged < 45 years

[4] During the first 10-years follow-up

[5] The ALSWH recruited three cohorts aged 18-23, 45-50 and 70-75 so the age distribution is not continuous

Table 2. Risk factor exposure prevalence, hazard ratios and fractions of breast cancers for premenopausal women avoidable by change in exposure over 10-years follow-up

Risk factors[1]	PR[2]	HR (95% CI)[3]	P for trend	Risk factor category change	PAF (95% CI)
Alcohol consumption			0.001		
1. 0 drinks/day	52%	1		2-4 → 1	12.6 (4.3, 20.2)
2. < 1 drink/day	29%	1.26 (1.04, 1.52)		4 → 2	1.4 (-0.9, 3.5)
3. 1-2 drinks/day	13%	1.29 (1.03, 1.62)		4 → 3	1.2 (-1.2, 3.5)
4. > 2 drinks/day	6%	1.52 (1.14, 2.03)			
Oral contraceptives (OCs), duration of use			0.02		
1. Non-current	73%	1		2, 3 → 1	7.3 (-0.3, 14.3)
				3 → 1	7.1 (0.3, 13.5)
2. Current, < 5 years	5%	1.03 (0.57, 1.88)		3 → 2	6.4 (-8.8, 19.4)
3. Current, ≥ 5 years	22%	1.34 (1.04, 1.73)			
Joint risk factors					
> 0 drinks/day and current OC use ≥ 5 years	59%				18.8 (9.1, 27.4)

CI (Confidence Interval); HR (Hazard Ratio); OC (Oral Contraceptive); PAF (Population Attributable Fraction); PR (Prevalence)

[1] Body fatness, physical activity and breastfeeding were not signficantly associated with breast cancer risk for premenopausal women

[2] Prevalence from AusDiab (Australian Diabetes, Obesity and Lifestyle) Study

[3] Age, study, alcohol consumption, and oral contraceptive use

Table 3. Risk factor exposure prevalence, hazard ratios, and fractions of breast cancers for postmenopausal women avoidable by change in exposure over 10-years follow-up

Risk factors[1]	PR[2]	HR (95% CI)[3]	P for trend	Risk factor category change	PAF (95% CI)
Body fatness (BMI)			< 0.001		
1. < 25.0 kg/m^2	42%	1		2, 3 → 1	12.8 (7.8, 17.5)
2. 25.0-34.9 kg/m^2	49%	1.21 (1.11, 1.32)		3 → 2	2.1 (0.3, 3.8)
3. ≥ 35.0 kg/m^2	9%	1.49 (1.26, 1.76)			
Alcohol consumption			0.002		
1. 0 drinks/day	42%	1		2, 3 → 1	6.6 (1.5, 11.4)
				3 → 1	4.4 (1.6, 7.2)
2. < 1 drink/day	32%	1.07 (0.96, 1.19)		3 → 2	2.7 (-0.6, 5.8)
3. ≥ 1 drink/day	26%	1.18 (1.06, 1.31)			
MHT, duration of use			< 0.001		
1. Non-current	86%	1		2-4 → 1	6.9 (4.8, 8.9)
				3, 4 → 1	6.9 (4.9, 8.9)
				4 → 1	6.4 (4.5, 8.3)
2. Current, < 1 year	1%	0.99 (0.63, 1.54)			
3. Current, 1-4 years	2%	1.24 (1.01, 1.51)		4 → 3	4.0 (0.9, 7.0)
4. Current, ≥ 5 years	11%	1.62 (1.43, 1.84)			
Joint risk factors					
BMI ≥ 25.0 kg/m^2, > 0 drinks/day and current MHT use	87%				24.2 (17.6, 30.3)
BMI ≥ 25.0 kg/m^2, ≥ 1 drink/day and current MHT use ≥ 1 year	75%				22.5 (16.9, 27.7)
BMI ≥ 25.0 kg/m^2, ≥ 1 drink/day and current MHT use ≥ 5 years	74%				22.1 (16.5, 27.3)

BMI (Body Mass Index); CI (Confidence Interval); HR (Hazard Ratio); MHT (Menopausal Hormone Therapy); NHS (National Health Survey); PAF (Population Attributable Fraction); PR (Prevalence)

[1] Physical activity (overall, vigorous physical activity) and breastfeeding were not signficantly associated with breast cancer risk for postmenopausal women

[2] Prevalence from LADY (Learning how Australians Deal with menopause sYmptoms) Survey

[3] Age, study, BMI, alcohol consumption, MHT use, nulliparity, and height

Table 4. Exposure prevalence, hazard ratios and fractions of cancer for postmenopausal women attributable to modifiable exposure by effect modifying factors

Effect modifier Risk factor categories	**Subgroup 1**		**Subgroup 2**		**Subgroup 3**		**Subgroup**	
	PR	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95%**
Body fatness (BMI)		**< 25 kg/m^2**		**≥ 25 kg/m^2**				
1. Non-current MHT use	84%	1	87%	1				
2. Current MHT use, < 1 year	1%	1.20 (0.64, 2.24)	1%	0.84 (0.45, 1.56)				
3. Current MHT use, 1-4 years	3%	1.19 (0.88, 1.63)	2%	1.26 (0.97, 1.64)				
4. Current MHT use, ≥ 5 years	12%	1.89 (1.58, 2.25)	10%	1.41 (1.18, 1.67)				
PAF (3, 4 → 1)[2]		10.4* (6.8, 13.8)		4.5 (2.1, 6.9)				
PAF (4 → 1)[2]		9.8* (6.4, 13.1)		4.1 (1.7, 6.4)				
Alcohol consumption		**0 drinks/day**		**< 1 drink/day**		**≥ 1 drink/day**		
1. Non-current MHT use	88%	1	85%	1	83%	1		
2. Current MHT use, < 1 year	1%	0.79 (0.39, 1.59)	1%	1.13 (0.50, 2.53)	1%	1.24 (0.55, 2.78)		
3. Current MHT use, 1-4 years	2%	1.36 (1.02, 1.80)	3%	0.93 (0.60, 1.43)	3%	1.35 (0.93, 1.95)		
4. Current MHT use, ≥ 5 years	10%	1.34 (1.09, 1.66)	11%	1.74 (1.39, 2.18)	13%	1.87 (1.52, 2.31)		
PAF (3, 4 → 1)[2]		3.8# (1.1, 6.4)		7.3 (3.3, 11.1)		11.1# (6.7, 15.4)		
PAF (4 → 1)[2]		3.2# (0.6, 5.7)		7.5 (3.7, 11.1)		10.4# (6.2, 14.4)		
Socio-economic status (SES)		**SES quintile 1 (low)**		**SES quintile 2**		**SES quintile 3**		**SES quintil**
1. Non-current MHT use	86%	1	88%	1	86%	1	86%	1
2. Current MHT use, < 1 year	1%	0.51 (0.12, 2.01)	0.5%	0.28 (0.04, 1.97)	0.5%	0.78 (0.25, 2.42)	1%	2.22 (1.14, 4
3. Current MHT use, 1-4 years	1%	1.06 (0.65, 1.72)	2%	0.81 (0.46, 1.45)	4%	1.08 (0.66, 1.76)	2%	1.25 (0.81, 1
4. Current MHT use, ≥ 5 years	11%	1.28 (0.94, 1.73)	9%	1.59 (1.18, 2.15)	10%	1.70 (1.30, 2.24)	12%	1.77 (1.37, 2
PAF (3, 4 → 1)[2]		3.1[#] (-1.3, 7.4)		5.1 (0.7, 9.3)		6.7 (2.2, 11.1)		8.6 (3.8, 13.1
Alcohol consumption		**0 drinks/day**		**< 1 drink/day**		**≥ 1 drink/day**		
1. BMI < 25 kg/m^2	36%	1	44%	1	48%	1		
2. BMI 25-34.9 kg/m^2	51%	1.25 (1.09, 1.42)	49%	1.42 (1.19, 1.69)	46%	1.01 (0.86, 1.20)		
3. BMI ≥ 35 kg/m^2	13%	1.47 (1.18, 1.84)	7%	1.78 (1.28, 2.46)	6%	1.29 (0.84, 1.99)		
PAF (2, 3 → 1)[2]		15.6 (7.6, 22.9)		20.7 (11.3, 29.1)		2.1***** (-6.7, 10.1)		
Educational attainment		**Low**		**Intermediate**		**High**		
1. BMI < 25 kg/m^2	37%	1	42%	1	48%	1		
2. BMI 25-34.9 kg/m^2	53%	1.35 (1.20, 1.51)	48%	1.28 (1.05, 1.56)	44%	0.87 (0.71, 1.07)		
3. BMI ≥ 35 kg/m^2	10%	1.75 (1.43, 2.15)	10%	1.47 (1.02, 2.13)	7%	0.67 (0.37, 1.21)		
PAF (2, 3 → 1)[2]		20.2 (13.5, 26.3)		15.0 (4.1, 24.5)		-8.5***** (-19.4, 1.4)		
Age		**< 65 years**		**≥ 65 years**				
1. BMI < 25 kg/m^2	42%	1	41%	1				
2. BMI 25-34.9 kg/m^2	48%	1.13 (0.99, 1.27)	51%	1.31 (1.15, 1.49)				
3. BMI ≥ 35 kg/m^2	10%	1.29 (1.03, 1.60)	9%	1.83 (1.41, 2.38)				
PAF (2, 3 → 1)[2]		7.9 (0.9, 14.4)		18.3* (11.1, 24.9)				
Breastfeeding[3]		**Never**		**Ever**				
1. 0 alcoholic drinks/day	57%	1	41%	1				
2. < 1 alcoholic drinks/day	26%	0.83 (0.61, 1.15)	33%	1.16 (1.02, 1.33)				
3. ≥ 1 alcoholic drinks/day	18%	0.77 (0.54, 1.08)	26%	1.32 (1.16, 1.51)				
PAF (2, 3 → 1)[2]		-9.6 (-21.7, 1.4)		12.1* (5.6, 18.2)				

PAF (3 → 1)[2]	-4.8 (-10.9, 0.9)	7.4***** (3.7, 10.9)

BMI (Body Mass Index); CI (Confidence Interval); HR (Hazard Ratio); MHT (Menopausal Hormone Therapy); PAF (Population Attri
* Burden for this subgroup differs from burden for other subgroup(s); # Burden between these two subgroups differs, i.e. the 95% conf
the PAF estimates for these subgroups does not include zero
[1] Age, study, BMI, alcohol consumption, MHT use, nulliparity, and height
[2] PAF and 95% confidence interval for the exposure modification
[3] Among parous women only
Note: some percentages do not add up to 100 because of rounding

Table 1. Characteristics of the individual and pooled cohort and external data sources

Characteristic	Cohort data							Prevalence data			
	MCCS	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**45&Up**	**Pooled**	**AusDiab**[1]	**LADY**[2]	**NHS**[3]	
Baseline year(s)	1990-1994	1992-1993	1996	1999-2000	1999-2003	2006-2009	1990-2009	1999-2000	2013	2001	2014-2015
State/Territory	VIC	NSW	All	All	SA	NSW	All	All	All	All	All
Pre-menopausal women											
Population (n)	7,666	77	21,052	2,518	854	15,016	47,183	2,527		4,965	3,455
Incident breast cancer cases (n)[4]	181	2	186	30	7	234	640	-		-	-
Deaths (n)[4]	72	3	145	24	12	64	320	-		-	-
Age in years at baseline, median (interquartile range)	45 (42-48)	51 (50-53)	22[5] (20-46)	38 (33-43)	36 (29-40)	48 (47-50)	46 (22-48)	38 (32-38)		32 (25-38)	31 (25-38)
Post-menopausal women											
Population (n)	14,615	1,891	13,419	2,592	778	103,074	136,369		3,564		3,097
Incident breast cancer cases (n)[4]	414	49	407	78	25	1659	2,632		-		-
Deaths (n)[4]	683	308	2,327	329	92	4,702	8,441		-		-
Age in years at baseline, median (interquartile range)	61 (56-65)	67 (60-74)	72 (70-73)[5]	64 (57-71)	66 (60-73)	63 (57-71)	63 (57-71)		64 (59-67)		66 (60-74)

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); LADY (Learning how Australians Deal with menopause sYmptoms) survey; MCCS (Melbourne Collaborative Cohort Study); NHS (National Health Survey); NSW (New South Wales); NWAHS (North West Adelaide Health Study); SA (South Australia); VIC (Victoria)

[1] The AusDiab study was used as the primary source to generate exposure prevalences for premenopausal women. The study population differs from that used for the cohort analyses as there are no exclusions

[2] The LADY study was used as the primary source to generate exposure prevalences for postmenopausal women

[3] Menopausal status based on age criteria only, i.e. women aged ≥ 55 years are considered postmenopausal and women aged < 45 years premenopausal

[4] During the first 10-years follow-up

[5] The ALSWH recruited three cohorts aged 18-23, 45-50 and 70-75 so the age distribution is not continuous

Table 2. Risk factor exposure prevalence, hazard ratios and fractions of breast cancers for premenopausal women avoidable by change in exposure over 10-years follow-up

Risk factors[1]	PR[2]	HR (95% CI)[3]	P for trend	Risk factor category change	PAF (95% CI)
Alcohol consumption			0.001		
1. 0 drinks/day	52%	1		2-4 → 1	12.6 (4.3, 20.2)
2. < 1 drink/day	29%	1.26 (1.04, 1.52)		4 → 2	1.4 (-0.9, 3.5)
3. 1-2 drinks/day	13%	1.29 (1.03, 1.62)		4 → 3	1.2 (-1.2, 3.5)
4. > 2 drinks/day	6%	1.52 (1.14, 2.03)			
Oral contraceptives (OCs), duration of use			0.02		
1. Non-current	73%	1		2, 3 → 1	7.3 (-0.3, 14.3)
				3 → 1	7.1 (0.3, 13.5)
2. Current, < 5 years	5%	1.03 (0.57, 1.88)		3 → 2	6.4 (-8.8, 19.4)
3. Current, ≥ 5 years	22%	1.34 (1.04, 1.73)			
Joint risk factors					
> 0 drinks/day and current OC use ≥ 5 years	59%				18.8 (9.1, 27.4)

CI (Confidence Interval); HR (Hazard Ratio); OC (Oral Contraceptive); PAF (Population Attributable Fraction); PR (Prevalence)

[1] Body fatness, physical activity and breastfeeding were not signficantly associated with breast cancer risk for premenopausal women

[2] Prevalence from AusDiab (Australian Diabetes, Obesity and Lifestyle) Study

[3] Age, study, alcohol consumption, and oral contraceptive use

Table 3. Risk factor exposure prevalence, hazard ratios, and fractions of breast cancers for postmenopausal women avoidable by change in exposure over 10-years follow-up

Risk factors[1]	PR[2]	HR (95% CI)[3]	P for trend	Risk factor category change	PAF (95% CI)
Body fatness (BMI)			< 0.001		
1. < 25.0 kg/m^2	42%	1		2, 3 → 1	12.8 (7.8, 17.5)
2. 25.0-34.9 kg/m^2	49%	1.21 (1.11, 1.32)		3 → 2	2.1 (0.3, 3.8)
3. ≥ 35.0 kg/m^2	9%	1.49 (1.26, 1.76)			
Alcohol consumption			0.002		
1. 0 drinks/day	42%	1		2, 3 → 1	6.6 (1.5, 11.4)
				3 → 1	4.4 (1.6, 7.2)
2. < 1 drink/day	32%	1.07 (0.96, 1.19)		3 → 2	2.7 (-0.6, 5.8)
3. ≥ 1 drink/day	26%	1.18 (1.06, 1.31)			
MHT, duration of use			< 0.001		
1. Non-current	86%	1		2-4 → 1	6.9 (4.8, 8.9)
				3, 4 → 1	6.9 (4.9, 8.9)
				4 → 1	6.4 (4.5, 8.3)
2. Current, < 1 year	1%	0.99 (0.63, 1.54)			
3. Current, 1-4 years	2%	1.24 (1.01, 1.51)		4 → 3	4.0 (0.9, 7.0)
4. Current, ≥ 5 years	11%	1.62 (1.43, 1.84)			
Joint risk factors					
BMI ≥ 25.0 kg/m^2, > 0 drinks/day and current MHT use	87%				24.2 (17.6, 30.3)
BMI ≥ 25.0 kg/m^2, ≥ 1 drink/day and current MHT use ≥ 1 year	75%				22.5 (16.9, 27.7)
BMI ≥ 25.0 kg/m^2, ≥ 1 drink/day and current MHT use ≥ 5 years	74%				22.1 (16.5, 27.3)

BMI (Body Mass Index); CI (Confidence Interval); HR (Hazard Ratio); MHT (Menopausal Hormone Therapy); NHS (National Health Survey); PAF (Population Attributable Fraction); PR (Prevalence)

[1] Physical activity (overall, vigorous physical activity) and breastfeeding were not signficantly associated with breast cancer risk for postmenopausal women

[2] Prevalence from LADY (Learning how Australians Deal with menopause sYmptoms) Survey

[3] Age, study, BMI, alcohol consumption, MHT use, nulliparity, and height

Table 4. Exposure prevalence, hazard ratios and fractions of cancer for postmenopausal women attributable to modifiable exposure by effect modifying factors

Effect modifier	**Subgroup 1**		**Subgroup 2**		**Subgroup 3**		**Subgroup 4**		**Subgroup 5**	
Risk factor categories	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**	**PR**	**HR (95% CI)[1]**
Body fatness (BMI)		**< 25 kg/m^2**		**≥ 25 kg/m^2**						
1. Non-current MHT use	84%	1	87%	1						
2. Current MHT use, < 1 year	1%	1.20 (0.64, 2.24)	1%	0.84 (0.45, 1.56)						
3. Current MHT use, 1-4 years	3%	1.19 (0.88, 1.63)	2%	1.26 (0.97, 1.64)						
4. Current MHT use, ≥ 5 years	12%	1.89 (1.58, 2.25)	10%	1.41 (1.18, 1.67)						
PAF (3, 4 → 1)[2]		10.4* (6.8, 13.8)		4.5 (2.1, 6.9)						
PAF (4 → 1)[2]		9.8* (6.4, 13.1)		4.1 (1.7, 6.4)						
Alcohol consumption		**0 drinks/day**		**< 1 drink/day**		**≥ 1 drink/day**				
1. Non-current MHT use	88%	1	85%	1	83%	1				
2. Current MHT use, < 1 year	1%	0.79 (0.39, 1.59)	1%	1.13 (0.50, 2.53)	1%	1.24 (0.55, 2.78)				
3. Current MHT use, 1-4 years	2%	1.36 (1.02, 1.80)	3%	0.93 (0.60, 1.43)	3%	1.35 (0.93, 1.95)				
4. Current MHT use, ≥ 5 years	10%	1.34 (1.09, 1.66)	11%	1.74 (1.39, 2.18)	13%	1.87 (1.52, 2.31)				
PAF (3, 4 → 1)[2]		3.8# (1.1, 6.4)		7.3 (3.3, 11.1)		11.1# (6.7, 15.4)				
PAF (4 → 1)[2]		3.2# (0.6, 5.7)		7.5 (3.7, 11.1)		10.4# (6.2, 14.4)				
Socio-economic status (SES)		**SES quintile 1 (low)**		**SES quintile 2**		**SES quintile 3**		**SES quintile 4**		**SES quintile 5 (high)**
1. Non-current MHT use	86%	1	88%	1	86%	1	86%	1	84%	1
2. Current MHT use, < 1 year	1%	0.51 (0.12, 2.01)	0.5%	0.28 (0.04, 1.97)	0.5%	0.78 (0.25, 2.42)	1%	2.22 (1.14, 4.31)	1%	1.08 (0.45, 2.63)
3. Current MHT use, 1-4 years	1%	1.06 (0.65, 1.72)	2%	0.81 (0.46, 1.45)	4%	1.08 (0.66, 1.76)	2%	1.25 (0.81, 1.92)	2%	1.79 (1.27, 2.52)
4. Current MHT use, ≥ 5 years	11%	1.28 (0.94, 1.73)	9%	1.59 (1.18, 2.15)	10%	1.70 (1.30, 2.24)	12%	1.77 (1.37, 2.30)	12%	1.70 (1.32, 2.18)
PAF (3, 4 → 1)[2]		3.1[#] (-1.3, 7.4)		5.1 (0.7, 9.3)		6.7 (2.2, 11.1)		8.6 (3.8, 13.1)		9.6[#] (4.8, 14.1)
Alcohol consumption		**0 drinks/day**		**< 1 drink/day**		**≥ 1 drink/day**				
1. BMI < 25 kg/m^2	36%	1	44%	1	48%	1				
2. BMI 25-34.9 kg/m^2	51%	1.25 (1.09, 1.42)	49%	1.42 (1.19, 1.69)	46%	1.01 (0.86, 1.20)				
3. BMI ≥ 35 kg/m^2	13%	1.47 (1.18, 1.84)	7%	1.78 (1.28, 2.46)	6%	1.29 (0.84, 1.99)				
PAF (2, 3 → 1)[2]		15.6 (7.6, 22.9)		20.7 (11.3, 29.1)		2.1***** (-6.7, 10.1)				
Educational attainment		**Low**		**Intermediate**		**High**				
1. BMI < 25 kg/m^2	37%	1	42%	1	48%	1				
2. BMI 25-34.9 kg/m^2	53%	1.35 (1.20, 1.51)	48%	1.28 (1.05, 1.56)	44%	0.87 (0.71, 1.07)				
3. BMI ≥ 35 kg/m^2	10%	1.75 (1.43, 2.15)	10%	1.47 (1.02, 2.13)	7%	0.67 (0.37, 1.21)				
PAF (2, 3 → 1)[2]		20.2 (13.5, 26.3)		15.0 (4.1, 24.5)		-8.5***** (-19.4, 1.4)				

Age		**< 65 years**		**≥ 65 years**
1. BMI < 25 kg/m^2	42%	1	41%	1
2. BMI 25-34.9 kg/m^2	48%	1.13 (0.99, 1.27)	51%	1.31 (1.15, 1.49)
3. BMI ≥ 35 kg/m^2	10%	1.29 (1.03, 1.60)	9%	1.83 (1.41, 2.38)
PAF (2, 3 → 1)[2]		7.9 (0.9, 14.4)		18.3* (11.1, 24.9)
Breastfeeding[3]		**Never**		**Ever**
1. 0 alcoholic drinks/day	57%	1	41%	1
2. < 1 alcoholic drinks/day	26%	0.83 (0.61, 1.15)	33%	1.16 (1.02, 1.33)
3. ≥ 1 alcoholic drinks/day	18%	0.77 (0.54, 1.08)	26%	1.32 (1.16, 1.51)
PAF (2, 3 → 1)[2]		-9.6 (-21.7, 1.4)		12.1* (5.6, 18.2)
PAF (3 → 1)[2]		-4.8 (-10.9, 0.9)		7.4**#** (3.7, 10.9)

BMI (Body Mass Index); CI (Confidence Interval); HR (Hazard Ratio); MHT (Menopausal Hormone Therapy); PAF (Population Attributable Fraction); PR (Prevalence)
* Burden for this subgroup differs from burden for other subgroup(s); # Burden between these two subgroups differs, i.e. the 95% confidence interval of the difference of the PAF estimates for these subgroups does not include zero
[1] Age, study, BMI, alcohol consumption, MHT use, nulliparity, and height
[2] PAF and 95% confidence interval for the exposure modification
[3] Among parous women only
Note: some percentages do not add up to 100 because of rounding

While several potentially-modifiable behavioural risk factors have been identified for breast cancer, estimates of the preventable future breast cancer burden are still lacking. Based on a large prospective pooled Australian cohort, here the authors reveal that regular alcohol consumption is the leading modifiable cause of breast cancer burden for premenopausal women (12.6%). Using the latest exposure prevalence information, the authors rank body fatness as the leading cause of preventable breast cancer burden for postmenopausal women (12.8%), with regular alcohol consumption also contributing substantially (6.6%). The findings provide evidence to support targeted and population-level cancer control activities in Australia and beyond.