

## Short communication

# Should lifestyle modifications be promoted to prevent breast cancer?

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Observational data indicate that diet and exercise are related to breast cancer risk and, together with alterations in reproductive patterns, may account for the marked increase in incidence of breast cancer seen worldwide [1]. An example of the increase in breast cancer comes from Iceland, where there are good long-term medical records [2]. Since the 1920s the incidence of breast cancer has increased fourfold, and interestingly the penetrance of the *BRCA2* founder mutation has increased from 20% to 80% during this time period, indicating an effect of lifestyle not only on sporadic but also on genetic breast cancer.

There is no clear evidence that any particular component of diet increases breast cancer risk with the exception of alcohol [3]. However, there is evidence from observational studies that weight gain, particularly between the ages of 20 and 50 years, is associated with increased risk for breast cancer; a 20 kg increase in weight is associated with a doubling of risk compared with women whose weight remains stable [4]. An overview of exercise studies indicated that regular moderate exercise is associated with a reduction in risk of about 30% compared with no or minor exercise [5]. Thus, their observational studies indicate that risk is related to diet and exercise, but the important question is whether there is any evidence that changing lifestyle reduces risk.

Animal studies of changing dietary composition (for example, a change in fat content) without reducing calories have been inconclusive [6]. The only large-scale randomized dietary composition intervention trial is the Women's Health Initiative Dietary Modification Trial. This trial was established in 1992 to test whether reducing dietary fat content to about 20% of calories from fat, increasing fruit and vegetables to five or more portions per day, and grains to more than six portions per day could reduce breast cancer. Women were randomly assigned to the dietary modification intervention group (40%

[ $n = 19,541$ ]) or to the control group (60% [ $n = 29,294$ ]). All women were postmenopausal, between the ages of 50 and 79 years [7]. After a period of follow-up of 6 to 8 years, there were no significant reductions in breast or other cancers or in the incidence of new cases of diabetes or cardiovascular disease [7-9]. Most of the dietary change targets were not met and compliance with the intervention fell from 57% at 3 years to 31% and 18% at 6 and 9 years, respectively. This study was well funded and well performed by a large number of professionals at 40 expert clinical centres throughout the USA. The results indicate that the intervention is not effective or that it is not possible to test such interventions in humans because of lack of compliance [10].

Although alterations to dietary composition have not been shown to be effective, multiple studies in rodents indicate that energy restriction reduces spontaneous breast cancer considerably. An overview of 14 studies of energy restriction in mice compared with *ad libitum* feeding revealed a reduced incidence of spontaneous breast cancer in the animals by a mean of 55% (95% confidence interval = 0.69 to 0.41) [11]. The reduction in risk was detected irrespective of the type of calories restricted (for instance, from fat, carbohydrate, or protein), the age of the mice at initiation of energy restriction, or the duration of energy restriction (the shortest duration was 38 weeks).

In humans, weight loss with energy restriction is observed irrespective of the type of calories restricted, but there are no randomized trials of energy restriction versus *ad libitum* feeding to prevent breast cancer [12]. Two observational studies indicate reduction in postmenopausal breast cancer risk in women who voluntarily elect to lose weight and maintain the loss. In the Iowa Women's Health Study, women who lost 5% or more of their body weight before the menopause and those who lost it after the menopause

IER = intermittent energy restriction.

reduced their risks for postmenopausal breast cancer by 40% and 25%, respectively [13]. In the Nurses Health Study (NHS), women who lost 10 kg or more after the menopause reduced their risk for breast cancer by 56% (95% confidence interval = 0.21 to 0.86,  $p = 0.01$ ) [4].

The data from the Iowa Women's Health Study and Nurses Health Study suggest that intentional and maintained weight reduction reduces risk. However, these women may have had reduced risk for other reasons, and randomized controlled trials of energy restriction versus *ad libitum* feeding are required to show formally an effect of energy restriction on risk. Such a trial may be impossible to perform because it is well known that compliance in energy restriction studies is poor. In a recent overview of randomised dietary trials 36% of women dropped out before 6 months, and longer term compliance is even poorer [14]. The same observations may well also apply to formal randomized studies of exercise [5].

Because energy restriction is effective in rodents and may be in humans, it seems worthwhile to continue thinking of this approach but the energy restriction regimen must be simple to apply and easy to undertake in order to reduce the cost of, and increase compliance with, any proposed randomized trial. One possible approach is to use intermittent energy restriction (IER), in which a very low calorie diet is given for a short period each week and an *ad libitum* diet is used for the remaining days. In rodents, IER is as effective as or more effective than continuous energy restriction. IER has also been shown to improve biomarkers such as leptin [15] and cell proliferation [16]. In premenopausal women at risk for breast cancer, we demonstrated in a randomized trial that IER (reduction of calories for 2 days per week) is as effective as continuous energy restriction in terms of weight reduction and biomarkers of risk such as serum insulin, sex hormone-binding globulin and androgens [17]. IER has also shown benefit in nonrandomized studies with respect to weight control and control of other diseases such as diabetes and asthma [18,19]. If an acceptable IER regimen can be found, then it would appear appropriate to design a randomized trial (versus *ad libitum* feeding) with breast cancer as an end-point.

It seems likely that part of the marked increase in the incidence of breast cancer is related to increases in dietary calorie intake and reduction in exercise over the past century. Alteration to dietary composition does not appear to be a viable approach to preventing breast cancer. Randomized studies in rodents and observational studies in women suggest that energy restriction and exercise may be viable approaches to breast cancer prevention, but they will need to be subjected to standard randomized clinical trials with breast cancer as the end-point.

### Competing interests

The authors declare that they have no competing interests.

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