

Mini Review

## DIET AND BREAST CANCER: EXPERIENCES FROM THE MALMÖ DIET CANCER COHORT

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*The Malmö Diet Cancer (MDC) group is a population-based cohort (n = 28 098) among Malmö inhabitants, aged 45–73 years at the time of baseline examinations in 1991–1996. Data collection regarding socio-demography, anthropometry and lifestyle was extensive, and included non-fasting blood samples. A high validity diet history was used to determine the usual diet. Information regarding cancer morbidity and mortality from the Swedish Cancer Registry is assessed yearly. Findings support the accepted hypotheses that a lifetime overexposure to sex hormones (modern reproductive patterns) and obesity promote postmenopausal breast cancer. Also, women with high intakes (compared to low intakes) of fibre, folic acid and fermented milk products have lower risk of postmenopausal breast cancer. High intakes of alcohol and energy-adjusted fat are associated with increased risk. Also, high intakes of dried soup-sauce-powders and of fried potatoes are associated with increased breast cancer risk. The MDC has two unique assets: the high validity dietary data and the well maintained bio bank. Since a multitude and diverse processes likely contribute to chronic disease the active use of biomarkers has become increasingly important to nutrition epidemiology. Clear information about the diet-breast cancer link is important to many women, because unlike reproductive factors diet is changeable throughout the lifecycle.*

**Key words:** diet, foods, nutrients, breast cancer, epidemiology.

Baseline examinations were conducted from March 1991 to October 1996 for the Malmö Diet Cancer (MDC), a prospective cohort in the third largest city of Sweden (Berglund, Elmståhl *et al.* 1993). A major objective of the study was to clarify whether a western dietary pattern could be linked to certain forms of cancer whilst taking other lifestyle and socio-economic factors into account. Another broad question was to explore if observed epidemiological associations were influenced by disease processes like oxidative stress and the activity in DNA-repairing systems, and if such processes could be linked to the dietary composition. There were also some major reasons why a large population-based study was established in Malmö. The Malmö University Hospital, the only referral hospital for the catchment area, has a long tradition of epidemiological research and a well-established Department of Pathology with high autopsy rates. The cancer morbidity and mortality rates are greater for Malmö compared to other parts of Sweden.

MDC participants were recruited through news-paper advertisements, flyers and direct mail invitations. All Malmö inhabitants aged 45–73 years (n = 75 000) were invited. Among the source population 30 000 women and men joined the MDC study. Each participant was required to visit the study centre twice. Direct measurements of anthropometrics and body composition (using a bio impedance

methodology), and non-fasting blood samples were collected at the first visit. Participants completed a structured extensive socio-demographic questionnaire at home. Data on dietary habits were collected through a modified diet history methodology, combining a questionnaire and a seven-day-menu book completed at home. At the second visit the usual diet was determined in a one-hour dietary interview. The high relative validity of the dietary data is a unique feature of the MDC (Riboli *et al.*, 1997; Thiébaud *et al.*, 2008). The food information was converted to nutrient intake data using the food-nutrient database originating from the Swedish National Food Administration (PC KOST2-93). Current use of dietary supplements and drugs was recorded in the menu book. Blood samples were separated into five fractions; serum and plasma fractions were frozen and stored at –80 °C. Information on cancer morbidity and mortality from the Swedish Cancer Registry is assessed yearly. Complete data from the baseline examinations are available for a total of 28 098 participants.

The reports from the MDC cohort support the accepted hypotheses that a lifetime overexposure to sex hormones (“modern” reproductive patterns) and obesity promote post-menopausal breast cancer (WCRF/AICR 2007) (Lahmann *et al.*, 2003).

In addition, women in the MDC with high energy adjusted intakes (compared to low intakes) of fibre, folic acid and fermented milk products have lower risk of postmenopausal breast cancer (Mattisson *et al.*, 2004; Wirfalt *et al.*, 2005; Sonestedt *et al.*, 2008). In contrast, high alcohol and energy-adjusted fat intakes (Wirfalt *et al.*, 2002), especially from vegetable oil based margarines, are associated with increased breast cancer risk after menopause (Wirfalt *et al.*, 2005). Moreover, we have observed that high intakes of dried soup-sauce-powders and of fried potatoes are associated with increased breast cancer risk (Wirfalt *et al.*, 2005) (Sonestedt *et al.*, 2008).

One project identified the type of breast tumours at the time of diagnosis (i.e., estrogen and progesterone receptor status (ERPR) from patient journals), and here we observed that the associations between food sources of fat was different depending on tumour type. Vegetable oil-based margarines (Multivariate HR: 1.34; 95%CI: 1.06–1.70), and dried soup- and sauce-powders (Multivariate HR: 1.37; 95%CI: 1.04–1.79) were associated with increased risk of breast tumours low in hormone receptors (i.e., ER-PR-), but fermented and regular milk and were associated with reduced risk, and dried soup- and sauce-powders with increased risk of tumours rich in hormone receptors (i.e., ER+PR+) (Wirfalt *et al.*, 2011).

Women in the MDC at the higher end of the folate intake distribution (i.e., the 5<sup>th</sup> quintile, median 302 µg) were consuming folate close to the recommended levels, and these women had lower risk of breast cancer (Multivariate HR: 0.56; 95%CI: 0.35–0.90) (Ericson *et al.*, 2007). We have also observed that the genetic factors influence the association between folate intake and breast cancer risk. Polymorphisms of the enzyme methylenetetrahydrofolate reductase (MTHFR) that metabolises folate have been associated with reduced activity. We hypothesized that the single nucleotide polymorphisms (SNPs) 677CT and 1298AC of MTHFR could modify the association between folate intake and breast cancer. Subsequently, our study indicated that women homozygote for the T-allele of the 667 CT polymorphism had increased risk of breast cancer at high folate intakes (Ericson *et al.*, 2009b) and when plasma levels were elevated (Ericson *et al.*, 2009a). About 10% of the population have this genetic variant. This association is particularly visible in women consuming folic acid supplements. Similar associations are not seen in women heterozygote for the T-allele and those homozygote for the C-allele (Ericson *et al.*, 2009a; 2009b).

Enterolactone (ENL) is formed from dietary lignan by the gut micro flora. We have specifically examined ENL in plasma (P-ENL). Women with high intakes of fruits and berries and fibre-rich bread have high levels of P-ENL. These women were more likely to be physically active and more educated. In contrast, women with low levels were more likely to be current smokers and obese. Thus high P-ENL could indicate healthier lifestyle and/or be a marker of fibre-rich diets (Sonestedt *et al.*, 2008). When comparing women with high P-ENL to those with low levels (median

split analysis) a significantly lower risk of postmenopausal breast cancer was observed (Multivariate HR: 0.75; 95%CI: 0.58–0.98). Also, high P-ENL level was specifically associated with reduced risk for breast tumours with high concentration of ER-alfa and low concentration of ER-beta (Multivariate HR: 0.59; 95%CI: 0.41–0.86) (Sonestedt *et al.*, 2008).

Epidemiological studies need dietary data of very high validity to draw quantitative conclusions and evaluate many factors simultaneously in multivariate analysis. However, since the physiological and pathological responses to diet involve a multitude and diverse processes, the active use of biomarkers (e.g. of dietary intake, of disease processes and of genetic variation) has become increasingly important to ascertain the impact of diet. Therefore, the MDC cohort study has two unique assets of great value to nutrition epidemiology: the dietary data of very high relative validity and the well-maintained bio bank.

The positive associations between high fat intakes and breast cancer risk are in line with animal experiments (Fay *et al.*, 1997; Ip, 1997), and some epidemiological studies (Wolk *et al.*, 1998) (Thiébaud *et al.*, 2009; Murff *et al.*, 2011). In addition, the findings regarding ERPR-status of tumours suggest that depending on the food source of fat both non-hormonal and hormonal mechanisms may be involved in breast tumour development. High alcohol intake is an established risk factor for postmenopausal breast cancer (WCRF/AICR 2007), thus the positive alcohol association was expected.

Since folate is a coenzyme of importance in the metabolism of amino acids and nucleotides, dietary folate intakes may influence cancer development through the involvement both in synthesis and repair of DNA. However, current epidemiologic evidence linking folate intake to breast cancer risk is not conclusive. The overall folate intake level in the Swedish population is low, compared to other populations where fortification with folic acid is common. Thus, when comparing our findings with other populations, both the overall intake level and chemical form must be taken into consideration.

All fiber-rich foods contain lignans, which are metabolized by the gut microflora into ENL and enterodiol (i.e., mammalian phytoestrogens with potential anti-estrogen influences), and then absorbed and metabolized. ENL shows similarities with the endogenous estrogen and may protect against breast cancer through binding to the estrogen receptors (ER), or competition with endogenous estrogen for the ERs (Sonestedt *et al.*, 2008; Sonestedt *et al.*, 2009). ERbeta is thought to inhibit the formation of ERalfa (Sonestedt *et al.*, 2008). Our observations may suggest that breast tumours with high concentration of ERalfa and low concentration of ERbeta (i.e.ERalfa+ERbeta-) may be more susceptible to the anti-estrogenic effects of enterolactone. In addition, our observation of a protective association with fermented milk is similar to that of a Dutch study, which found that women combining low fat intakes with high in-

takes of fermented milk and dietary fibre had significantly lower breast cancer risk (Van't Veer *et al.*, 1991). We hypothesize that diets combining fibre-rich foods and fermented milk may facilitate fermentation in the gut, and thus the formation of mammalian phytoestrogens, which potentially have breast cancer protective influences. However, more research is still needed in this area.

To conclude, the results indicate that an overall “Westernized” diet low in plants foods, but high in various food products (like powdered soups and sauces, deep-fried potatoes and margarines) is linked to increased risk of postmenopausal breast cancer. The conclusion that breast cancer protection is observed with diets based on naturally fibre-rich foods (providing essential nutrients and other bio active substances with health benefits) is supported by other studies, specifically a recent systematic review of dietary patterns and breast cancer (Brennan *et al.*, 2010). Several physiological processes likely contribute to these observations. Similar to others, our findings do not support the use of supplements. Clear information about the diet-breast cancer link would be of importance to many women, because unlike reproductive factors dietary habits are changeable throughout the lifecycle.

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#### KRŪTS VĒZIS UN UZTURA FAKTORI: MALMES VĒŽA PACIENTU KOHORTAS PĒTĪJUMA PIEREDZE

Malmes vēža pacientu kohortas populācijas pētījumā (n = 28 098) iekļauti Malmes pilsētas iedzīvotāji vecumā no 45 līdz 73 gadiem, laika periodā no 1991. gada līdz 1996. gadam. Tika iegūti sociodemogrāfiskie, antropometriskie, dzīvesveida, uzņemta uztura dati, kā arī asins paraugi. Pētījuma rezultāti rāda, ka krūts vēža risku palielina aptaukošanās, alkohols, tauki, sausās zupas, cepti kartupeļi uzturā, bet samazina šķiedrvielas, folskābe un fermentēti piena produkti. Sievietēm ir svarīgi zināt, kā uzturs ietekmē krūts vēža attīstību, jo uzturs ir ietekmējams riska faktors.