**The Prevention of Breast Cancer**

The discovery and rapid application of the testing for mutations in the BRCA1 and the BRCA2 genes. The major drive is for setting up breast cancer reducing services. Now multiple other gene mutations and single nucleotide polymorphisms (SNPs) related to breast cancer have been discovered. Between 20% and 54% of women who develop breast cancer have a family history of the disease. There **are high penetrance genes that account for around 5% of breast cancer.** For the rest of the estimated **27% to 30% of breast cancers due mainly to hereditary factors** there are more polygenic inheritance moderate risk alleles of lower risk common variance.

There are **non-modifiable risk factors** such as **nulliparity** **or late-age first pregnancy** and more modifiable risk factors such as lack of breast feeding, weight gain and lack of exercise. Despite our knowledge of such factors many women develop breast cancer.

One estimate has been that the increase in breast cancer in western world compared to African women is related to **reduction in family size and lack of breast feeding**. In **Iceland there was a fourfold increase in the risk of sporadic breast cancer between 1920 and 2000. Such a rapid ch**ange in risk is most likely to be epigenetic related to lifestyle and unspecified environmental factors. Lifestyle factors may also influence the penetrance of genetic changes.

The UK NICE guidelines indicate that **women at high risk of breast cancer greater or equivalent to 30% lifetime risk** should **be offered preventative treatment with Tamoxifen or Raloxifene** and that women at moderate risk greater than or equal to 1:6 lifetime risk or greater than 3% 10-year risk aged 40 years should be considered for five years of treatment. One breast cancer risk model is the Tyrer-Cuzick model. It asks for a three-generation family history and factors of lifestyle such as first pregnancy and body mass index. Another model is the Claus tablets concerning family history and risk factors. By far the majority of breast cancers are diagnosed in women over the age of 50 years. In the **UK NHS breast screening programme women undergo mammography every three years between the ages of 50 and 70.**

**Currently Tamoxifen is the only approved preventative therapy available for premenopausal women** and is given for five years. In postmenopausal women NICE guidelines indicate that five years treatment with either Tamoxifen 20 mg a day or Raloxifene 60 mg a day may be considered. Since the gynaecological toxicity of Tamoxifen far outweighs the minimal gynaecological issues seen with Raloxifene **Tamoxifen is usually given to those who have had a prior hysterectomy and Raloxifene to those with an intact uterus.**

**Five years of treatment with Tamoxifen result in a 33% or hazard ratio 0.67 reduction in breast cancer risk. For Raloxifene there was an overall 66% reduction in risk, 0.34**, the trial being for four years and continued for a further four years in core extension, so total of **eight years of treatment resulted in the 66% reduction risk**. The RUTH trial resulted in a 44% risk reduction, 0.56 hazard ratio. The STAR randomised trial directly compared two selective SERMs, demonstrates that Raloxifene was less effective than Tamoxifen after seven years of follow-up for invasive breast cancer, hazard ratio 1.24. Since Raloxifene is poorly absorbed around 2% and has a short half-life of 27 ? hour compliance is particularly important compared to Tamoxifen. In the second four years as compared to the first four years with Raloxifene there was a greater reduction risk of 0.34 compared with 0.41. When explaining the risk reduction to women at high and moderate risk of breast cancer it seems reasonable to suggest an overall 40% reduction in breast cancer risk and to indicate that **Raloxifene is somewhat less effective than Tamoxifen**. In one trial at the Royal Marsden HRT was allowed in women who had severe hot flushes. The reduction in risk was less in this trial. **Addition of HRT Tamoxifen resulted in abrogation of its effectiveness,** hazard ratio 0.87 versus non-use 0.55. Both **Tamoxifen and Raloxifene maintain bone density** and **reduce cholesterol** although the latter has not formally been shown to be useful in terms of reduction in cardiovascular event.

**Side effects of preventative therapy with Tamoxifen**. Patients will have changes in their menses but also **uncommonly fibroids and ovarian cyst may enlarge**, cause pain and may result in the need for gynaecological intervention. **Endometrial cancer is not induced by Tamoxifen in premenopausal women**. **In postmenopausal women there is an increased risk of endometrial cancer**. During five-year treatment of postmenopausal women there was a **3.76 fold increase.** That is still an uncommon occurrence. 4 out of 3575 women in controls and 15 out of 3579 women treated.

Five women in the Tamoxifen group died from endometrial cancer compared with none in the placebo group. Therefore it seems wise to **avoid Tamoxifen for breast cancer prevention in postmenopausal women with a uterus and to consider Raloxifene or an aromatase inhibitor instead**. In the MORE trial there was no difference in the development of endometrial cancer between Raloxifene and the control. The toxicity of Raloxifene is different from Tamoxifen since with Raloxifene there is an increase in ankle swelling and aches in legs**.**  **Both drugs increase the risk of DVT and pulmonary embolism two to three fold**. As yet *Tamoxifen has shown no significant increase on breast cancer specific survival or death without a prior diagnosis of breast cancer.*

***In IBIS-I Tamoxifen was associated with a non-significant and small increase in death****, 166 controls and 182 Tamoxifen.* **The main target for Tamoxifen** is *where endometrial cancer risks are minimal – in women under 50 years old and thromboembolic events less common*. In the MORE trial there was a non-significant 37% reduction in death and in the core trial a non-significant 23% reduction in death in women treated with Raloxifene. There are two other SERMs that look impressive but have not been developed by their companies. **Aromatase inhibitor,** these are **superior to Tamoxifen for preventing relapse and reducing the incidence of contralateral breast cancer after primary surgery for breast cancer.**  **Both *Exemestane and Anastrozole* have now been tested in randomised placebo controlled trials in postmenopausal women at increased risk of breast cancers**. Both Exemestane and Anastrozole have now been tested in randomised placebo controlled trials in postmenopausal women at increased risk of breast cancer. Exemestane reduce relapse by 65% after median follow-up of 36 months. **Anastrozole reduce relapse by 50% after median follow-up of seven years. Women taking AIs have more joint aches and flushes than controls and this also results in a reduction in bone density.** The latter **is prevented by the use of bisphosphonate**. They have not yet been evaluated for prevention. It would need to be emphasised that *these drugs are bone toxic and an increase in rare conditions such as carpal tunnel.*

**Bisphosphonates**. Two studies in women with osteoporosis reported a 30% lower breast cancer incidence in users versus non-users of bisphosphonate. In another study there was no significant reduction. **Metformin**, widely used to treat type 2 diabetes works **by targeting the enzyme AMP-activated protein kinase (AMPK)** which induces muscles to take up glucose from the blood. They showed a possible reduction in breast cancer with Metformin.

**Aspirin.** Consistently been shown to be preventative in a number of cancers. Studies suggest a reduction of **breast cancer risk by about 10% for Aspirin and possibly a little bit more for Ibuprofen.** Similar results have been found with NSAIDs and COX-2 inhibitors.

**Lifestyle change, weight gain, lack of exercise and excess alcohol.** Overweight is linked to 12 other cancers including endometrial, gallbladder, renal, rectal, postmenopausal breast, pancreatic, thyroid, colon, oesophageal cancer and leukaemia, multiple myeloma and non-Hodgkin’s lymphoma and malignant melanoma. Sedentary lifestyle is also linked to colorectal and endometrial cancer let alone diabetes and cardiovascular risk and dementia.

**Alcohol** is also linked to **oropharyngeal, oesophageal, laryngeal, colorectal, liver, stomach, gallbladder, pancreas and lung cancer**.

Weight control. **Weight gain of** **more than 20 kg between 18 and 50 resulted in a doubling of breast cancer risk.** In the Iowa Women’s Health Study maintained weight loss of over 5% after the menopause reduce risk by over 25% compared with women who continue to gain weight. **Other studies reported a 60% reduction in risk with a greater than 15% weight loss.**

**Exercise.** Currently only 4% of adult women are meeting the current exercise guidelines of **150 minutes of moderate or 75 minutes of vigorous physical activity per week.** A review of 73 observational studies indicated that **moderate to vigorous physical activity reduces breast cancer risk by an average of 25%** in pre and postmenopausal women compared to inactive women. The optimal level of physical activity for breast cancer reduction may be greater than the current recommendation of 150 minutes per week.

**Alcohol**. It is estimated that **breast cancer risk is increased by 7% to 10% for each additional unit increase in alcohol intake per day.** Increased risk is thought to be related to acetaldehyde-induced DNA strand deletion chromosomal aberrations and DNA adducts with downregulation of tumour suppressor gene BRCA1 and increased oestrogen and prolactin receptor activities.

**Alcohol before the first pregnancy is particularly associated with cumulative risks**. Unresolved questions include the specific effects of binge drinking, whether dietary folate can reduce the excess risk of alcohol intake, 1 L a day of alcohol is linked to breast cancer risk however zero alcohol intake is not recommended **as light drinking is consistently linked to reduction in overall 17% and cardiovascular 20% mortality.** Quality of work in some units suggests that breast cancer risk is not a primary driver for weight control in women who are at an increased risk of breast cancer. Key motivators for more immediate concerns were appearance, well-being and self-esteem.

**Risk-reducing mastectomy reduces the risk of breast cancer by 90 to 95% with a skin-sparing mastectomy** approach. RRM, **NICE advice is uptake of surgical option for women with a greater than 30%** **lifetime risk.** **The risk reducing oophorectomy prior to natural menopause** has been associated with around 50% reduction **in breast cancer risk in BRCA1 and 2 mutation carriers.**

**Breast Cancer and Population Targeted Breast Screening.**

After 13 years of follow-up of several meta-analysis of the randomised controlled trials of breast cancer the **combined risk ratio was 0.81 corresponding to a 19% reduction of breast cancer mortality for women invited to screening** compared to women not invited for screening, **age 40 to 74 at entry.** **The independent UK panel** on breast meta-analysis suggested a relative risk ratio of 0.8, ie a **reduction of risk of 20%.** In the meta-analysis in the US preventive task force there **was relative risk of 0.85 for women 39 - 49 years of age, risk reduction of relative risk of 0.86 for women in 50 - 59** and women aged60 - 69 of 0.68 a relative risk reduction for. These *randomised control trials were conducted in the 70s and 80s, now imaging techniques are much better as is treatment.*

Cohort studies and meta-analysis of recently conducted case controlled studies found combined odds ratio for breast cancer mortality of 0.52 in screened women versus unscreened women age 50 and older. When looked at the combined overall risk for invited versus not invited woman it was 0.69. Observational studies are more prone to bias than randomised control studies*. A greater breast cancer mortality reduction tends to be associated with observational studies.*

**Evidence for screening women under 50, ie 40 - 49** there is a lower breast cancer incidence, lower sensitivity of mammography due to great breast density and possibly more aggressive tumour growth. Meta-analysis of the randomised control **studies mortality reduction of 15 to 17**%. The largest cohort study from *Sweden in women aged 40 to 49 years showed a relative risk reduction of 0.74 in women invited for screening and those not invited for screening. The actual relative risk reduction for women attending screening was 0.71.*

**Evidence for benefit of screening of women above 70***. The* ***Swedish two-county trial*** is the only one that looked at this age group. Women aged 70 to 74 at entry were invited to two screening rounds. There was a noticeably significant effect even though the **relative risk was 0.76**. The confidence intervals were 0.44 to 1.33.

**Overdiagnosis screen detection of cancer** that would never have presented clinically during women’s lifetime in the absence of screening is considered **the most adverse outcome of breast cancer mammography** screening. The absolute number of overdiagnosed cases reflects the excess of cancers diagnosed in women who are invited to screening or attend screening relative to women who are not invited to screening. Treatment of an overdiagnosed cancer will not improve disease prognosis and therefore considered to be harmful. The estimated overdiagnosis rates vary by a factor of 3.5 in different RCTs. An adequate calculation should take into account ductal carcinoma in situ, DCIS. *Analysis and trials suggest an excess cancer as a portion of cancer diagnosed woman invited to screening to be around 11% during the lifetime and approximately 19% during the screening period.*

**Different countries mammographic screening policies**. There is relatively consistency in general on a minimum age range of 50 to 69 with a **screening interval of two years** and the trials are conducted screening of three-year intervals high interval cancers were present. Despite this evidence women are screened once every three years in the UK and Malta, seems this is wrong*. In the* ***UK the attendance rate is about 73%*.** Finland has a very high attendance rate of 85 and Ireland 78% but most other countries other than the Netherlands which showed 80% are lower than UK. Slovenia interestingly is at 76%. With reference to the UK programme of screening at three years compared to two years was presented in the international agency for research on cancer 2002 volume 7 breast cancer screening in IARC Handbooks of Cancer Prevention, Vainio and Bianchini. **Recall rates** range from 1% in Netherlands to 7% in the UK**. Women under 50 are invited in 12 European countries** and five of these programmes invite women from age 40. Recently published study of breast cancer mortality in a Canadian breast cancer screening programme reported that the average breast cancer mortality rate was 40% lower among participants **relative** to expecting mortality rate based on non-participants. **In Australia the upper age limit is currently extended from 69 to 74 years**. In the United States preventative services task force have stated that the additional benefits and harm to **screening age in women aged 75 years or older are not clear due to lack of evidence of this group.** In Italy there is a tailored breast screening trial with screening strategy based in women between 45 and 49 on the breast density.

**New technologies in breast cancer screening**.

**Digital breast tomosynthesis DBT**, **three dimensional tomographic images** created from multiple low-dose projection images acquired by moving the x-ray tube of limited angular range. The overall *mean glandular dose of DBT radiation is comparable to that of conventional two-dimensional imaging.* Typically the reconstruction has a 1 mm slice thickness. *Conventional 2D images are acquired at the same time*, DBT has a potential to overcome the primary limitation of standard 2D mammography that arises from overlapping of fibroglandular breast tissueimproving diagnostic accuracy by differentiating benign and malignant features of the increasing lesion conspicuity particularly in dense breasts. Several publications primarily from the USA based studies have reported **superiority of full field digital mammography FFDM plus DBT combo** imaging compared to 2D alone in increased sensitivity and specificity and reader performance. Some results however are conflicting. **The Oslo tomosynthesis** screening trial reported a ***27% increase in cancer detection rates*** *across all breast density and a 15% decrease in false positive recall rate using DBT in combination with 2D mammography compared to 2D mammography alon*e. The population based **STORM screening study** showed **a 34% increase in cancer detection across all age groups** in breast density and their potential to **reduce the false positive recall by 17%.**

Reading time was doubled. Current ongoing studies include the *Malmö Breast Tomosynthesis Screening Trial.* Preliminary results indicated 15% increased in sensitivity with DBT but a slight 3% increase in recall rate. A large retrospective US study by Friedewald reported 29% increase in cancer detection rate. Results from the TOMMY trial, large retrospective reading studies showed a modest 2% ? improvement in cancer detection rates for DBT plus 2D compared with 2D alone but a clear improvement of 11% in specificity. 2D mammography is definitely required for optimal microcalcification assessment as well as the DBT. The use **of DBT in combination with 2D requires an approximate doubling radiation exposure**. It is possible to generate a synthetic 2D image from a single DBT scan, the accuracy of DBT in synthetic 2D is currently being evaluated within the Oslo trial.

Although mammography is the only imaging modality to have proven to decrease breast cancer mortality in screening of a general population one of its limitations lies in the imaging of **40% women classified as having dense breasts.** **Women with dense breast tissue have a four-six fold increased risk of breast cancer** partly due to independent risk factors for breast cancer but also decreased sensitivity of mammography in this cohort of women. In the US there is “Are You Dense Campaign”. This requires radiologist to inform women of their breast density and suggest alternative screening option. Magnetic resonance imaging, **MRI has been recommended as screening tool for women with dense breasts** but it has drawback in terms of costs, accessibility

*Many studies have demonstrated that* ***ultrasound is a good screening tool for women with dense breasts****. It has relatively low patient tolerance and lack of ionising radiation.* Berg et al demonstrated that **55% more cancers were detected in women with dense breasts using handheld ultrasound and mammography than mammography alone**. With the breast ultrasound there is a relatively low positive predictive value. **Recent advance is automated whole breast ultrasound AWBUS.**  The aim being to eliminate operator dependence. In some systems a large transducer panel is placed over the breast with gentle compression allowing the whole breast to be imaged at the same time. **Multiple studies have demonstrated equal or greater lesion detectability with AWBUS than with handheld** imaging. Some studies suggested increased cancer detection rate from **3.8 per 1000 with mammography alone to 7.2 per 1000 with both modalities.** The increasing requirements for better imaging in women with dense breasts means that AWBUS is likely to evolve and to be a useful adjunct to mammography in widespread screening.

In summary in terms of a previously discussed **digital breast tomosynthesis shows increased sensitivity compared to just 2D alone between 2 and 27% and improve specificity of 11 to 15% in screening situations.**

**Contrast Enhanced Digital Mammography**

**Contrast enhanced digital mammography** **CEDM** utilises the fact that leaky basement membranes and vessels and malignancy make tissues more contrast material ? that is injected intravenously to look for results and tumour enhancement. 1.5 ml/kg of iodine based contrast medium was injected. There was a temporal technique. When the breast is compressed initially while a non-enhanced image is taken prior to contrast injectionwith compression a series of post contrast images obtained over a period of three to five minutes.

The non-contrast images are then subtracted from the contrast image. The resultsare **promising in women with dense breasts particularly.** Only one breast can be imaged at a time. Contrast enhanced spectral imaging obtains high and low-energy images after the administration of intravenous contrast. Standard mammographic image as well as high-energy image. These can be added together to eliminate the background breast parenchyma demonstrated areas of contrast enhancement within the breasts. CESM has been compared with MRI demonstrating equally accurate breast cancer detection rates with MRI and CESM but fewer false positive rates for CESM.

The drawbacks to CESM include higher radiation dose of 54% greater than standard mammography at 2.65 **mGY** and the use of IV contrast and the time taken. There is also the issue of not currently being able to perform a biopsy with this method and may limit its value as a screening tool.

**MRI Scan**

MRI, demonstrates **superior sensitivity to both mammography and ultrasound in the detection of breast cancer** and is now routinely used for multiple indications including screening of women at high-risk breast cancer. Its use is currently limited due to imaging time and cost and availability as well **as false positive rates.**  There are techniques aimed to improving these with **3D maximum intensity projection MIP image and the first post contrast T1-weighted image (FAST)** disposing the further sequences that are mostly used for lesion characterisation. MRI analysis alone has a sensitively negative predictive value of 98.9% which can be increased to 100% with associated FAST images. Currently there is only indirect evidence of screening with MRI and they effect survival. Further perspective multisensory trials are required to look at this.

**Breath testing**.

 Molecular biomarkers have been increasingly investigated for a detection of early malignancy. Breath analysis as a potential screening method has been non-invasive and relatively easy to use. **Exhaled human breath c**ontains a large number **of volatile organic compounds (VOC**), some of which are produced endogenously by the body’s metabolism and may be detected by methods including gas chromatography and mass spectrometry.

It is proposed that due **to increased oxidative stress caused by malignancy alkanes and alkane derivatives are produced by reactive oxygen species ROS** (causing lipid peroxidation of cell membrane). The detection of **VOC** – volatile organic compounds in exhaled human breath is already used in the clinical setting for detection of Helicobacter pylori and asthma, nitric oxide. Numerous potential biomarkers for detection of breast cancer being proposed have shown promising results in the detection of malignancy. **It is not necessarily specific for breast malignancy** in particular. Larger studies are required.

**Dr Michael Sandberg**