

MENOPAUSE MATTERS

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HRT & breast cancer

Hormone replacement therapy (HRT) is used by millions of women for the relief of menopausal symptoms. It does this effectively as well as having an array of other effects (see following summary) but it also has contra-indications and potential harms which seem to dominate discussions and grab the headlines. The WHI trial will probably be the only randomised investigation for the foreseeable future as the numbers required for suitable power calculations to yield dependable results are considerable, the drug companies are not going to risk such product exposure and ethically it would be suspect.

The Million Women Study was observational and last year's Systematic Review and Meta-analysis was derived from pooled information of heterogeneous publications so current authoritative data are pertinent. The case control study from general practices in the UK is the most reliable so far and will most likely be the standard quoted for a number of years to come ([Vinogradova et al *BMJ* 2020 ;371:m3873](#)). The research covered nearly 100 000 women with breast cancer and matched them with nearly half a million controls between the ages of 50 and 79 years of age. It showed:

- About a third of all UK women had used some form of HRT in the preceding year
- Recent use was taken to be HRT within the last 5 years
- Long-term use was taken to be HRT for greater than 5 years
- All data were measured against base-line risk in never-users
- The estrogen-only HRT increase in risk was 1.15 (CI 1.09 to 1.21)
- The combined estrogen plus progesterone odds ratio was 1.79 (CI 1.73 to 1.85)
- Of the progestogens, norethisterone had the highest, and dydrogesterone the lowest risk
- Past long-term estrogen-only and past short-term combined therapy carried no forward risk
- Past long-term combined therapy did carry lingering risk
- There is no increased risk of dying from breast cancer by taking HRT

In real terms (not relative risk) the actual numbers were for women younger than 60 years:

Recent combined HT users – 22 extra cases per 10 000 or 0.2%
Past combined HT users – 5 extra cases per 10 000 or 0.05%
Recent estrogen only users – 3 extra cases per 10 000 or 0.02%

Your columnist's opinion – I genuinely have difficulty conceptualising odds as low as these, never mind conveying them to a woman in terms that are meaningful to her.

The smaller differences are the equivalent of a matchstick lying on the floor; to the height of a door.

The general population does not work out their risks of disease or disability or death (because that is what happens to other people). Epidemiological reasoning is not how Pat Public thinks about life and research shows "human beings are more attuned to anecdotes than hard data" which is not a criticism but how we aetiologically evolved ([Sundar *BMJ* 2020;371:m4121](#))

What I would like the statisticians to work out is the actual risk to a healthy woman of taking HRT for 5 years during her 50s. And while they are at it, could they also suggest how those 5 years would affect her cardiovascular health, her bone health and her haematological profile so we could present a balanced picture.

At present we have to put together packages of risks and benefits, adjusting these according to each woman's expectations and concerns. Yes, these data are helpful but we have to interpret them for the woman in front of us so the statistics provide a map but every woman has a different journey she wishes to envisage travelling.

Genomic approaches to breast cancer

Last month in Menopause Matters we described the potential of circulating metabolites in screening for endometrial cancer and asked what other applications would have clinical value.

Closely related to screening for tumour metabolites is the detection of circulating tumour DNA (ctDNA). Researchers have studied the levels of ctDNA in breast cancer patients and have related higher levels to poorer outcomes ([Cullinane et al JAMA Netw Open](#) 2020;3:e2026921). This prognostic measure appears applicable to early, late and metastatic disease and the serum levels will have the advantage of allowing treatment responses and tumour progression to be monitored.

Another genetic development is the study of "Repair Genes" in patients with breast cancer. Repair genes are responsible for "numerous cellular activities that repair DNA lesions and maintain genomic integrity, which are critical in preventing tumorigenesis" ([Zhang et al JAMA Netw Open](#) 2020;3:e2014622). Groups of these genes form "signatures", and by investigating if these DNA repair-related genes (DRGs) are present or not, clinicians can predict the overall survival of breast cancer patients. Researchers chose a set of 8 DRGs as a prognostic signature and tested over 1 000 women and the predictions were accurate for 3 and 5 years survival curves. This means that oncologists now have a novel risk-prediction model that will assist diagnostic accuracy and guide treatment strategies.

These are the promised application of genomics to clinical medicine and are prime examples of "precision medicine" in action.

Other HRT effects

HRT does have wide-ranging effects beyond breast cancer risk and these include haematological changes, bone metabolism (including osteoarthritis of the knees), genital morphology and function effects (including vaginal health and sexual health), mental function (including cognition, mood and dementia), skin changes ([Tucker G M](#) 2019) as well as muscle mass and strength.

Sarcopenia is defined as a loss of muscular contractile bulk and function with age which can lead to falls, fractures and disability. In a study from Korea ([Kim & Kim Menopause](#) 2020;27:506-11) it was demonstrated that prolonged HRT use "was associated with higher muscle mass and lower prevalence of sarcopenia in postmenopausal women."

The loss of estrogenic effect is apparent in voice changes which are thought to be due "to reduced vocal fold muscle bulk and incomplete glottal closure on phonation" ([Lin & Wang JAMA Otolaryngol Head Neck Surg](#) 2020;146:1045-53). HRT can result in better lubrication of the vocal cords and less disruption of their vibratory properties or hoarseness which some women find bothersome. Vitamin B injections have no effect on professional singers voices ([Shoffel-Havakuk et al JAMA Otolaryngol Head Neck Surg](#) 2020 doi:10.1001/jamaoto.2020.4026).

Sexually Transmitted Infections in young and old

"The 21st century has seen a global resurgence of sexually transmitted infections (STIs). From a nadir in the 1990s, the rates of gonorrhoea, syphilis, and chlamydia infections have increased substantially in high-income countries ..." These are the opening words to an authoritative review of STIs which is recommended reading to those in the field ([Williamson & Chen NEJM](#) 2020;382:2023-32).

In England last year ([Wise BMJ](#) 2020;370:m3425):

- Gonorrhoea cases increased by a quarter to the highest levels since records started more than a century ago
- The sharpest increases were noted in gay and bisexual individuals as well as in men who have sex with men
- Rates in heterosexual women also increased by a quarter
- Genital warts diagnoses are declining owing to HPV vaccinations

There have been previous studies linking Chlamydia infection with subsequent miscarriage but the findings have been inconsistent. A recent paper from Scotland reporting on more sophisticated and precise antibody checking for preceding Chlamydia has shown no correlation between prior infection and likelihood of miscarriage ([Horne et al JAMA Netw Open](#) 2020;3:e2018799).

Data from the United States on STIs:

Chlamydia and gonorrhoea infections continue to rise but the advent of point-of-care diagnostics for both are being hailed as significant steps forward in "one stop" diagnostics and treatment ([Van Der Pol et al JAMA Netw Open](#) 2020;3:e204819). Self-obtained vaginal swabs and on-the-spot testing takes 30 minutes and is proving to be a significant advance in clinics. These molecular tests are as accurate as formal investigations; can be done by non-laboratory-trained staff and allow precision diagnostics and appropriate treatment eclipsing the "syndromic approach".

- Adolescents and young adults presenting to U S Emergency Departments are a group who should be targeted for on-the-spot STI work-up ([Eckman et al JAMA Pediatr](#) 2020 doi. 10.1002/jamapediatrics.2020.3571)
- Pregnant women should have immediate treatment if diagnosed with syphilis to prevent the major increases in congenital syphilis occurring a present ([Kimball et al MMWR Report](#) 2020;69:661-5)
- Women who are diagnosed with gonorrhoea and chlamydia should be routinely tested for HIV as the rate of positive tests is well above those in regular testing facilities ([Henny et al Obstet Gynecol](#) 2020;136:1083-5).

Data from Europe on STIs:

Another report from Europe looks in depth at middle-aged adults (mean age 45 years old) sexual habits and preferences which reflects a wide range of attitudes, giving insights into the accepting, if not progressive attitudes existing in modern society in Belgium, The Netherlands and the UK ([The Sexual Health in over Forty-Fives \(SHIFT\) project](#)). The sociological aspects suggest a widening of monogamous boundaries in a group that were formerly perceived to be conservative or stable with resultant increase in STI risk which has reached record levels in this age-group. The authors are quoted as saying ""Given improvements in life expectancy, sexual healthcare needs to improve its intervention for older adults and vulnerable groups to provide a more utilised, knowledgeable, compassionate, and effective service."

Polyunsaturated Fatty Acids & health

Omega-3 fatty acids (PUFAs) have been in vogue for many years as supplements and show no sign of decreasing popularity. The global market of \$4 billion is predicted to double in the next 5 years but is there clear evidence that they have health benefits?

The latest trial has come to the conclusion that they have no value in patients at high risk of cardiovascular disease – even at adequate dosages and over a reasonable length of time – longer than 3 years ([Nicholls et al JAMA 2020 doi. 10.1001/jama.2020.22258](#)). Other trials have given heterogeneous results but it is unlikely that drug firms will have an appetite for more extensive and expensive research so any further investigations are problematic ([Curfman JAMA 2020 doi: 10.1001/jama.2020.22898](#)).

Certainly adding vitamin D to PUFAs does not do any good in older adults ([Bischoff-Ferrari et al JAMA 2020;324:1855-68](#)) so you can advise your patients to put their money where their legs are – rather than into the coffers of supplement manufacturers .

If you would like to listen to an authoritative interview on the latest about Covid vaccines got to:

<https://www.youtube.com/watch?v=V4xCLOYM3iE>

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Menopause Matters is a monthly review of matters menopausal that have recently appeared in the journals. It is produced for the South African Menopause Society and the summaries concentrate on clinical issues although some underlying patho-physiology will be included to ensure a scientific basis for the work. These summaries and opinions do not necessarily reflect the views of the S A Menopause Society.

The idea is derived from the Journal Article Summary Service (JASS) which summarises general O&G articles. Information about this service can be obtained from Athol Kent (atholkent@mweb.co.za) or from the JASS website www.getjass.com