JOURNAL ARTICLE SUMMARY SERVICE

August 2020

Cancer surveillance in older women

Colorectal cancer is the third most commonly diagnosed malignancy in women and the most lethal after lung and breast cancer. Despite this formidable burden of disease it is amenable to screening by a number of modalities and it has an age-related profile so it is possible for older women to follow a rational approach to surveillance.

Screening is recommended to start at 50 years but it is most strongly supported by data for those between the ages of 60 to 75 on a 5 yearly schedule of direct observation using sigmoidoscopy or colonoscopy. A conundrum arises in the very old (75+) who may gain more benefit because of the greater likelihood of positive findings on a purely age basis, but with a shorter subsequent life expectancy, they have less to gain. There is little guidance as to the risk of colonoscopy itself so the findings of a North American study are helpful (Causada-Calo et al *JAMA Netw Open* 2020;3:e208958).

Complications of colonoscopy rise with age being 3% in people younger than 75 and 7% in those older than 75 years. Other than age, risk factors are any cardiovascular, renal or hepatic disorders, smoking and obesity. Also to be taken into consideration are the benefits of detecting resectable early disease in the older group (1.5%) compared with the younger group (0.5%).

Editorial declaration: I have had screening colonoscopies as recommended for low-risk individuals over the years as I believe it to be an evidence-based test in terms of its diagnostic and therapeutic capabilities but I think I will now opt for faecal occult blood testing on my GP's advice into my dotage.

Hormone therapy & breast cancer

The use of hormone therapy at the time of the menopause transition and beyond has its protagonists and detractors. Most clinicians believe it is indicated and safe for the relief of menopausal symptoms for 5 years duration but is not recommended for long-term prophylactic use for bone protection, cardiovascular health or maintaining cerebral function.

It is unlikely that there will ever be a randomised controlled trial along the lines or magnitude of the Women's Health Initiative that began nearly 3 decades ago and was terminated for adverse outcomes. However the study has yielded consistent data on the relationship between estrogen and estrogen plus progesterone treatment and breast cancer over 20 years. (Chlebowski et al *JAMA* 2020;324:369-80). For women without a uterus who received estrogen only therapy, the incidence of breast cancer was reduced in the short and long-term – as were mortality rates from breast cancer. This is a counter-intuitive finding suggesting it could be used preventatively to reduce mortality but may need to be initiated "a little away from the menopause". Combined estrogen plus progesterone therapy was consistently associated with increases in breast cancer incidence but showed no significant difference in breast cancer mortality.

These outcomes are at variance to the findings of the Collaborative Group and the Million Women Study, both of which established raised risks of breast cancer incidence and mortality from estrogen only or combined hormone use. A woman's decision to embark on hormone therapy remains primarily her desire for symptomatic relief, her age and her individual risk of developing conditions such as cardiovascular or thromboembolic disease, osteoporosis or colorectal cancer (Minami & Freedman *JAMA* 2020;234:347-9).

Breast cancer management progress

Research into treatments for early breast cancer is leading to more enlightened approaches with better results. The initial surgery has become progressively less formidable with fewer mastectomies and more lumpectomies with post-operative irradiation to the breast and local tissue being the standard follow-up at present. But daily radiation over weeks of external beam radiotherapy is time-consuming and is an unrealistic option in disadvantaged situations so the alternative of a single dose of targeted irradiation at the time of the operation has been studied.

In a trial lasting more than a decade, over 1 000 patients were allocated to either intra-operative radiotherapy as a once-off procedure or serial conventional external beam radiotherapy usually over 30 days. It was conducted in the UK, Europe, Australia and North America (Vaidya et al *BMJ* 2020;370:m2836). There were no significantly different outcomes in local recurrences, disease-free or overall survival with lower mortality from other causes with the single therapy option suggesting fewer "regional" risks.

Editorial comment: *This is a significant advance for high, middle and low income health services. It seems the dogma that radiotherapy has to be given in multiple doses to the whole breast has been successfully challenged and another step taken in uncomplicating early breast cancer treatment with non-inferiority plus short and long-term advantages plus wider application possibilities.*

Hormone therapy and unexpected consequences

Women generally have higher-pitched voices than men – by an octave on average. Women's voices range from 165 to 255 Hz while men's voices are deeper at 85 to 155 Hz and the difference is classically attributed to the testosterone surge around puberty when boys' voices "break" as their vocal cords elongate and thicken.

Women's voices tend to change through the menopause transition, with lower estrogen levels leading to fewer glandular cells in the sub-epithelial layer of the vocal cords with resultant dryness and reduced vibratory properties. This produces a lower pitch and lesser projection which can impact on social situations and perceived attractiveness. It has been established that hormone therapy can affect a woman's fundamental frequency (with a raised pitch) and this has been measured at a mean 186 Hz in users and 175 in non-users (Lin & Wang *JAMA Otol H N Surg* 2020 doi. 10.1001/jamaoto.2020.2174).

Last year it was reported that menopausal hormone therapy was associated with a decreased prevalence of osteoarthritis of the knees is an observational study of substantial duration (Jung et al *Menopause* 2019;26:598-602). It is likely that other "indirect" effects of hormone therapy – both positive and negative will be uncovered. This does not necessarily make them indications for commencing treatment but they may be viewed as fringe benefits and certain women could find them cogent reasons for considering medication and it is important that clinicians stay informed of unanticipated outcomes.

Falls, fractures, menopause & medication

One of the scourges of growing old is the danger of falling and breaking bones. With increasing age comes bone fragility with the commonest and most researched topic being hip fractures about which new information is continuously emerging.

Women are living longer in the postmenopausal stage of their lives but, for individuals, is there an increase or decrease in age-related hip fractures? According to data from the ongoing Framingham Heart Study the incidence is decreasing which may be attributable to osteoporosis treatment or lifestyle changes (Swayambunathan et al *JAMA Int Med* 2020;e202975). Risk factors for hip fractures include smoking, heavy drinking, being underweight or obese and an early menopause, with reductions in the first two being coincident with the observed decrease in fracture rates which have dropped by about 5% per year for the last 4 decades.

Fragility fracture protection with bisphosphonates is undoubtedly effective in reducing breakages but adoption of their use has been retarded by reports of atypical femoral fractures – a situation researched in the US and showing a real association (Black et al *NEJM* 2020;383:743-53). The risk did increase with longer use then rapidly decreased on stopping the medication. The absolute risk of atypical fractures is low and very low in comparison with the prevention of hip fractures offered by bisphosphonates in general.

Denosumab is a monoclonal antibody used to treat osteoporosis in postmenopausal women and men at high-risk of fracture, but it should be used regularly, or vertebral and possibly other bone fracture risks can increase (Lyu et al *Ann Int Med* 2020:doi. 10.7326/M20-0882).

Who should receive preventative therapy? It is recommended that screening for osteoporosis by bone mineral density (BMD) measurement should take place in women 65 years or older and their fracture-risk calculated using algorithms. What is not clear is whether repeat BMD measurements make for a more accurate prediction of fracture risk or not. To answer the question researchers prospectively looked at a follow-up BMD test 3 years after the initial assessment and found it did not help discriminating between women who would or would not experience a subsequent fracture and the scientists state that second assessments at 3 years "should not routinely be performed" (Crandall et al *JAMA Int Med* 2020: doi.10.1001/jamainternmed.2020.2986).

Falls cause fractures and volumes have been written about their prevention but linking their occurrence in relation to hospitalisation is novel (Hoffman et al *JAMA Netw Open* 2020;3:e2013243). Falls increase in likelihood prior to, during and after hospital admissions so care-providers should be aware of events and medication that can potentially lead to situations of risk at these times – which is practical advice in the prevention armamentarium.

A factor associated with osteoporosis is a premature menopause but there is little that is known which affects the timing of this transition – or is there? Perfluoroalkyl substances (PFAS) are compounds widely used commercially and residentially as surfactant modifiers. They are similar to insecticides such as DDT and can contaminate water supplies. In women they are hormonally active in ways that are being researched with early results showing that those with the highest serum levels of 4 clusters of PFAS exposure experience their natural menopause on average 2 years earlier than those in the lowest cluster (Ding et al *J Clin E&M* 2020.doi.10.1210/clinem/dgaa303). This suggests there are environmental contaminants that can directly influence hormonal changes and subsequent osteoporosis and fracture risk.

The greatest preventative measure against fracture risk remains exercise.

Testosterone & depression

Women suffer from depression more commonly than men and it is often resistant to conventional antidepressant medication so some patients resort to hormonal therapy such as testosterone. Small studies and anecdotal evidence have shown mood improvements in non-formally diagnosed women with suggestions of higher energy levels and raised libido. More robust research has now been published using tight diagnostic criteria and outcomes that included MRI measurements of the anterior cingulate cortex, which is the region of the brain that is central in mood regulation (Dichtel et al *Am J Psychiatry* 2020.doi.10.1176/appi.ajp.2020.19080844).

The researchers used transdermal testosterone cream in 100 adult women with a mean age of 47 years or placebo and assessed depressive mood, fatigue and sexual function over 8 weeks. Depressed mood was reduced (from 26 points at commencement in both groups) to 15 in those receiving the testosterone application and 14 in those allocated to the inert substance, indicating a large placebo effect. Energy, sexual function and cingulate cortex activation showed no difference in the two study arms.

Although well tolerated, testosterone therapy for middle-aged women did not improve symptoms of depression nor did it combat fatigue or raise sexual function levels.

Fibroids and options

Women who have symptomatic fibroids suffer from a reduced quality-of-life and although there is an array of medical interventions available, the treatments are not always successful or well tolerated. Moving beyond medications, hysterectomy has been described as a "one size fits all" option that offers durable quality-of-life improvements but it is not acceptable for those who desire reproductive possibilities or wish to retain their bodily integrity (Stewart *NEJM* 2020;383:489-90).

Under these circumstances uterine artery embolization and myomectomy deserve consideration but it is a difficult decision between the two with little research offering direct comparisons. However, a head-to-head trial has been conducted in the UK giving guidance to clinicians putting options to their patients (Manyonda et al *NEJM* 2020;383:440-50). The FEMME trial recruited a heterogeneous group of women with a common problem – the wish to retain their uterus but seeking symptom relief after an inadequate response to medical therapy for their fibroid-related issues.

The fact that all the recruits were facing significant challenges was reflected in the large uterine volumes involved (a mean of 1 000+cm^3) and the procedural complications that ensued which occurred 1 in 4 patients across the board. Also, the number of live births was low following either intervention, being around 2%, but with a mean age of 40+ years, this is perhaps not unexpected.

The most telling results were the quality-of-life scores (100 being optimal) with 85 points in the myomectomy arm and 80 points in the embolization arm. These results were derived at the 2 year follow-up point so reliable comparisons can be made.

Preterm delivery & long-term maternal health

Preterm delivery rates run at about 10% worldwide and carry risks of morbidity and mortality to the offspring commensurate with the gestational age at birth. It is established that mothers of these children carry risks of cardiovascular and metabolic disease long past the pregnancy but it is not known if their life expectancy is affected.

A study from Sweden looked at all deliveries (more than 2 million) in that country over the last 4 decades and recorded the mother's longevity in relation to the degree of prematurity if she gave birth to a child at an early gestational age (Crump et al *BMJ* 2020;370:m2533). The researchers showed that if the woman had a preterm birth, her hazard ratio of premature death compared with a woman who delivered at term was 1.78 (CI 1.6 to 1.87) and the risk increased with earlier delivery.

Further analysis revealed that the association was not explained by shared genetic or environmental factors within families indicating underlying condition/s exacerbated by pregnancy or ongoing detrimental consequences of a complicated gestation. The data demonstrate a high-risk group whose members should have long-term follow-up and monitoring for chronic disorders that could potentially lead to their early demise.

Pre-induction Foley's catheter placement

If a nulliparous woman requires induction of labour near term but has an unfavourable cervical score, she is often given a "priming" procedure. A popular method is the insertion of a transcervical Foley catheter when she is admitted and prior to formal induction but a group of investigators explored whether a catheter placed as an outpatient the day prior to the elective induction would facilitate the process (Ausbeck et al *Obstet Gynecol* 2020 doi. 10.1097/AOG0000000000004041).

The objective was to reduce the admission/delivery interval while not increasing the risk of complications. A group of just over 100 women were randomly selected to out- or in-patient arms of the study – all of whom were at 39 weeks gestation. Those in the out-patient cohort had a mean shorter admission/delivery duration of labour than those treated as in-patients (17 hours v 21 hours). There were more admissions before scheduled induction in the out-patient group but otherwise the outcomes were not significantly different. Of note was the mean BMI of the entire cohort at greater than 30 and the caesarean section rates 24% and 32% respectively.

Covid & obstetrics

Although the Covid epidemic is abating in many countries, concerns remain about its effects on pregnancies. Women wish to know if it is safe to embark on a pregnancy, what dangers exist at different gestations or delivery and what risks there are to neonates. Evidence of safety or otherwise is appearing from sophisticated sources able to collate data rapidly and pass on their experiences.

From New York observers report that most pregnant women who tested positive for Covid remained asymptomatic but those who were affected had complexity of their outcomes commensurate with the severity of their symptoms (Khoury et al *Obstet Gynecol* 2020;136:273-82). Severity was linked to obesity and was reflected by higher preterm deliveries and raised caesarean delivery rates.

The English data showed increased stillbirth rates during the pandemic although the demises did not appear to be Covid-linked (Khalil et al *JAMA* 2020;324:705-6). The authors suggest indirect causes such as reticence to attend clinics – although this fear appears to be unfounded (Reale et al *JAMA* 2020 doi. 10.1001/jama.2020.15242), failing to report to obstetric units when danger signals arose or disruptions to staffing quotas.

Incidentally it appears breast-feeding is safe and should be encouraged – as is banked milk that is Holder pasteurised (Chambers et al *JAMA* 2020. doi. 10.1001/jama.2020.15580).

The trouble with cannabis – a wafting editorial meander

The trouble with cannabis is that people think it is a benign substance.

It is perceived to be a less dangerous drug than its fellow intoxicants, for example opioids (such as heroin and pethidine) and crack cocaine or fentanyl or alcohol. The reasons why it is thought to be innocuous are in part, the fault of a strange set of bed-fellows:-

- proponents of greater "enlightenment";
- people who wish to have the law relaxed so they can promote the cannabis industry for financial gain;
- the cigarette and alcohol companies who see a business opportunity;
- governments who anticipate considerable tax revenues;
- the medical profession, who are being duped into suggesting it is first-line medication for a select group of disorders (which it is not) and thereby giving it an "aura of medical respectability".

This is a formidable combination of forces which all see benefits from a fledgling industry that is projected, in the US alone, to be worth $66 billion in 5 years' time. It is in their interests to emphasize the "lesser danger" of cannabis relative to other mind-altering drugs, while promoting its sale and conveniently down-playing its immediate hazards and ignoring its potential long-term risks.

Why it's nice (and dangerous) to be "high"

For those who seek a temporary escape from reality, there is an attraction to using cannabis. In adults who wish to "remove themselves" from situations which they find oppressive or disheartening, a "trip or high" offers some respite from the daily grind. While under the influence of cannabinoids, personality changes can seem positive, such as:

- shy people feel released from their social constraints and become more gregarious, less concerned about how they come across and are able to mix socially;
- emotional constraints are less binding and people feel empowered to speak their minds, to be more forthright or "honest";
- feeling more liberated they may, for a while, become "more the person they want to be" – being less serious and more frivolous or adventurous. These are all the hallmarks of fewer checks and balances with a loss of inhibitions usually mediated by the pre-frontal cortex;
- they may also have a perception of greater insights or clarity of issues or even heightened powers of artistic appreciation or greater social acceptance.

There are however limitations and a potential downside to "seeing things differently":-

- emotional instability can ensue, with strong feelings – both positive and negative being juxtaposed or rapidly following each other, which is a confusing lability;
- loquaciousness may result in the expression of personal opinions without thought for the ramifications of their articulation;
- with fewer inhibitions in play users may be more amenable to suggestions of a risky nature that would not be accepted or agreed to under normal circumstances;
- with looser judgement, unusual behaviour can be embarked upon and it is not the optimal time to make decisions that may have long-term repercussions. Choices that are made with relational, financial, sexual consequences may later be regretted.

These possibilities often have an instant gratification element, together with a sense of excitement and derring-do – all of which have appeal during the experimentation of adolescence. With vulnerability, unrealistic suggestions can be accepted and exploitation can occur. A real example is the use of cannabis as a gateway drug to more well-known alternatives.

Empowerment, be it unrealistic or temporary, does carry a seductive element and this can feed the brain's reward centre. For those familiar with the first step of addiction, this will resonate clearly and cannabis is an addictive substance that begins the ensnarement of its victims by causing reward-centre stimulation.

Why it is likely to cause harm

Tetrahydrocannabinol (THC) is the active substance in cannabis flower preparations and concentrates but surprisingly little is known about the detrimental effects it can have. There is no agreed measure of its strength either inhaled or ingested although "mild" "strong" and "potent" are advertised on merchandise. Plasma concentrations can be measured but the effects on subjective intoxication, neurobehavioral factors, motor function and skill levels are highly variable and depend on a person's size, tolerance and age.

It is simply unknown if there are safe or dangerous levels below or above which function is unaffected or dangerous (Bidwell et al *JAMA Psychiatry* 2020;77:787-96). What is known is that with feelings of intoxication there is short-term memory impairment and poorer proprioception and balance function. The effects on motor vehicle driving ability are also unknown but there is circumstantial evidence of its harm. In areas of the United States where cannabis laws have been relaxed there are increases in traffic fatality rates comparing "before and after" statistics (Rosekind et al *JAMA Int Med* 2020. doi. 10.1001/jamaintmed.2020.1984, Santaella-Tenorio & Wheeler-Martin *JAMA Int Med* 2020;180:1061-8 and Kamer et al *JAMA Int Med* 2020; doi. 10.1000/jamainternmed.2020.1769).

It is used by some women in early pregnancy for nausea but evidence of its efficacy and safety are not documented. It is linked with growth restriction and preterm delivery so its use should be discouraged at any gestation according to leading societies. In the past the sins of the father fell on the children but, in this gender-neutral day and age maybe that idiom should include mothers.

There is an association between cannabis use and depression. It is commonly believed to be therapeutic despite studies showing its repeated use may worsen depressive symptoms and now temporal research reveals that "those with depression increased their rates of cannabis use significantly faster than those without depression" suggesting a spiralling scenario in the 30% of depressives in the United States who use cannabis regularly (Gorfinkel et al *JAMA Netw Open* 2020;3:e2013802).

Most concerning is the link between cannabis use and psychoses. This is the consensus view of experts who state that "Consistent evidence, both from observational and experimental studies, has confirmed the important role of cannabis use in the initiation and persistence of psychotic disorders." (Sideli et al *J Dual Diagn* 2020;16:22-42). Especially vulnerable are those with a family history or using it during adolescence "which is only too common" (Murray & Hall *JAMA Psychiatry* 2020;77:777-8).

From the public mental health point of view, any substance that increases the chances of psychoses being unmasked or created should be regulated.

Snippets

New spermicidal contraceptive

A new vaginal gel contraceptive has been registered in the US under the trade-name Phexxi© (Evofem Biosciences). It acidifies the vaginal milieu providing contraceptive cover if inserted prior to intercourse and has a Pearl Index rating of 28 pregnancies per 100 woman years which is comparable to other spermicidal preparations such as nonoxynol-9.

It contains lactic acid, citric acid and potassium bitartrate, so it may appeal to women seeking a non-hormonal product for over-the-counter pregnancy protection.

IUDs & adolescents with disabilities

Adolescents with physical, intellectual or developmental difficulties present a challenge of menstrual control and possibly contraception. Since levonorgestrel-containing intrauterine devices can provide both functions, their use in incapacitated young women is of interest to them and those who care for them.

Data from their use in 160 patients with a mean age of 16 years showed high continuation rates at one and five years of 95% and 73% with side effects and complications of less than 3% (Schwartz et al *Pediatrics* 2020;146:e20200016). The rates of amenorrhoea were of the order of 60%. Nearly all (96%) were inserted "in the operating room" presumably under sedation or general anaesthesia so with these provisos an option exists in assisting young women with disabilities.

Antibiotics and contraceptive effectiveness

It is well-known the enzyme-inducing antibiotics reduce the effectiveness of oral contraceptives (OCs) but what of antimicrobials that are not enzyme inducing? It seems they may also impede the success of OCs in preventing pregnancies (Aronson & Ferner *BMJ E-B M* 2020 doi. 10.1136/bmjebm-2020-111363).

Indeed, it was found that "Compared with control medicines, unintended pregnancies were seven times more commonly reported with antibiotics and 13 times more commonly reported with enzyme inducers" which implies that while taking any antibiotics, all OC takers should be warned of decreased reliability and be instructed accordingly.

HIV prophylaxis

Pre-exposure prophylaxis against HIV is remarkably effective if taken orally on a daily basis by at-risk individuals – with figures of 99% protection being quoted by the CDC. The difficulty is that daily tablet-taking is in many cases inconvenient with resultant less-than-desired benefit, although data from Africa showed infection rates of 0.35% with use where these had been 1.4% previously.

Long-acting injections offer a pragmatic alternative and an international study has demonstrated that they give 3 times the protection of the oral preparation in real world circumstances (Landowitz et al *World AIDS Conf* 2020). Given at 8 weekly intervals they can protect HIV naïve partners as well as being more private than the pill option.

Athol Kent

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Dear Colleague

Administration: you will have noticed that we now send JASS out as a PDF attachment. This is done to ensure you receive exactly what was published in the form intended.

However, if you would rather have it in MS Word document format, just let us know and we will place your name on an alternate distribution list and you will receive JASS the way you want it.

JASS this month leads with research concerning older women and some issues likely to be addressed by colleagues who see women in this age bracket because this group will continue to expand relatively as our population ages. The matters presented are practical and could be of interest for many different reasons.

I make no apologies for revisiting the cannabis story as it has a very high profile in the journals as more and more worrying data are published.

Together with other drugs – there are questions being asked about routine anonymous and personal testing in clinics – including ante-natal clinics.

Would you be in favour, and would you institute such invasions of privacy?
Are we there yet?

I sincerely hope not but much depends on your “catchment” area.

Kind regards

Athol Kent

Phone +27 21 686 4935 Fax 086 671 4755 Eddress atholkent@mweb.co.za

JASS questions for August 2020

True/False

1. Colorectal cancer is the third most lethal malignancy encountered in women _____
2. Intra-operative irradiation for early-stage breast cancer is just as effective as serial external beam irradiation given over 30 days _____
3. Post-menopausal hormone therapy is often found to raise the pitch of women's voices _____
4. Testosterone therapy is an effective form of treatment for depression in middle aged women _____
5. For the treatment of symptomatic fibroids, uterine artery embolisation gives double the quality-of-life subjective improvements compared with myomectomy _____
6. Compared with 40 years ago, the rate of hip fractures in the elderly is increasing _____
7. Bisphosphonate therapy reduces fracture rates in osteoporotic women _____
8. The use of cannabis has an important role in the initiation and persistence of psychoses _____
9. Pre-induction placement of a trans-cervical Foley's catheter on an out-patient basis reduces the length of labour in women being induced at term with an unfavourable cervix _____
10. Pre-exposure prophylaxis medication against HIV infection is now available in a depo-injection format _____

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