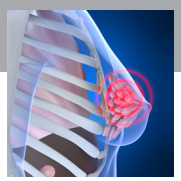




Bulletin Board

Women who undergo treatment for cervical and vaginal precancerous cells may be at increased risk of developing cancer in future

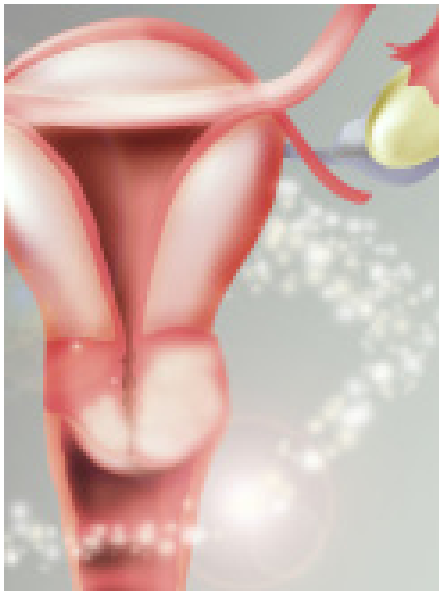
Recent findings have demonstrated that the risk of vaginal and cervical cancer development is higher in individuals who have previously undergone removal of precancerous cells. These women, who have had prior treatment for cervical intraepithelial neoplasia grade 3 (CIN3), may present with a higher probability of both development and mortality of vaginal and cervical cancers compared with the general population, although, investigators state that the risk is still low.

Screening to prevent cervical cancer – cytology screening – has been successful, proving to be an effective method of reducing cervical cancer mortality. The risk of developing cervical cancer is not eradicated; however, and women are invited to attend follow-up programs.

This new study, published in the *British Medical Journal*, is proposed to be the first to examine how cervical cancer-associated mortality risk, post-CIN3 treatment, is impacted by aging. The study utilized data from over 150,000 women with CIN3, with almost 150 presenting with vaginal cancer and over 1000 with invasive cervical cancer. Mortality rates caused by the diagnosed conditions in this sample were 53 and 302, respectively. These data were obtained from the Swedish Cancer registry, and the study was completed by investigators from Sahlgrenska University Hospital (Göteborg, Sweden) and the Karolinska Institute (Solna, Sweden).

The present study demonstrated that invasive cervical and invasive vaginal cancer risk increased with age in women who were treated for CIN3 in comparison to the general population. In particular, the increase was reported when the CIN3-treated women surpassed 60 years of age. The risk accelerated to over 100 per 100,000 women once the CIN3-treated women surpassed 75 years of age, with a correlation being highlighted between the higher risk of cancer and how recently in which women had received treatment. In contrast to the general population, the risk of cause-specific death more than doubled after 30 years post-CIN3 treatment.

The investigators of the study stress that CIN3 treatment does protect women from cervical cancer and that it is only a small number of patients who may later develop and die from the disease. It is concluded that the CIN3 treatment is beneficial for those patients with the CIN3 diagnosis, yet, increasing age following treatment and how recently the patient was treated does play a role in



Women's HEALTH

in the news...

- **Lead story:** Women who undergo treatment for cervical and vaginal precancerous cells may be at increased risk of developing cancer in future
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Future Medicine part of fsg

the accelerated risk of developing these cancers in future, and it is suggested that women undergo follow-up surveillance throughout their lifetime.

– Written by Elizabeth Webb

Sources: British Medical Journal press release: www.bmj.com/press-releases/2014/01/13/researchers-suggest-risk-cervical-or-vaginal-cancer-higher-women-previously; Björn Strander B, Hällgren J, Sparén P. Effect of ageing on cervical or vaginal cancer in Swedish women previously treated for cervical intraepithelial neoplasia grade 3: population based cohort study of long term incidence and mortality. *BMJ* 348, f7361 (2014).

Also featured on www.oncology-central.com

New approach developed for improved imaging of breast cancer

Engineers and radiologists at Dartmouth (NH, USA) are developing new approaches for MRI with near-infrared spectroscopy (NIRS), an emerging technique in diagnostic imaging for breast cancer.

Prior approaches for MRI/NIRS have used parallel plates and relied on custom breast molds for each patient. Now, biomedical engineers from the Thayer School of Engineering at Dartmouth have developed a new, more flexible, convenient and comfortable approach. The approach involves a set of eight light transmitting cables that can be adjusted to surround the breast with light tension. In a procedure that is nearly identical to clinical MRI, with the patient lying on their stomach, the breast hangs pendant through the holes of the MRI/NIRS breast coil.

The new method, described in *Academic Radiology*, combines synergistic attributes of concurrent dynamic contrast-enhanced MRI and NIRS with a new design of the clinical NIRS breast interface, which couples to a standard magnetic resonance breast coil and allows imaging of variable breast sizes. "We found that the new interface allowed us to target lesions more effectively than ever before," said Michael Mastanduno, corresponding author of the study, "Set-up time was faster and images were of higher quality."

Spectral information from eight healthy volunteers and two cancer patients showed that the new coupling system significantly improved examination utility, by allowing improved coupling of the near-infrared fibers to breasts of all cup sizes and lesion locations. These improvements were demonstrated over a range of breast sizes and normal tissue heterogeneity. "This work is a huge improvement on previous designs of MRI/NIRS systems," enthused Mastanduno, "All breast sizes and lesion locations can now be effectively imaged."

In addition, the Dartmouth MRI/NIRS offers increased coverage of the chest, giving providers improved visibility for 'hard-to-see' areas, meaning that lesions located in the axillary region and medial–posterior breast are now accessible to NIRS optodes. "Though there is more work to be done, this technology is promising for improving MRI's ability to distinguish cancer from benign abnormalities," concluded Mastanduno. The Dartmouth researchers have announced that the next step in research will test MRI/NIRS in women with suspicious lesions.

– Written by Ruth Williamson

Sources: Researchers developing new approach for imaging dense breasts for abnormalities: http://geiselmed.dartmouth.edu/news/2014/01/24_mri; Mastanduno MA, El-Ghussein F, Jiang S *et al.* Adaptable near-infrared spectroscopy fiber array for improved coupling to different breast sizes during clinical MRI. *Acad. Radiol.* 21(2), 141–150 (2014).

Also featured on www.oncology-central.com

Prophylactic mammary irradiation of unaffected breasts could reduce the incidence of second cancers by threefold

At present, long-term breast cancer survivors have an elevated risk of developing breast cancer in the contralateral breast. Due to of these risks, approximately 10–20% of breast cancer survivors in the USA undergo prophylactic mastectomy of their other breast.

Now, new results from researchers at Columbia University Medical Center (NY, USA) has suggested that breast cancer survivors can dramatically reduce this risk of developing cancer in their other breast, through treatment with moderate doses of radiation to the unaffected breast at the same time as receiving radiation therapy to the affected breast.

If the treatment works as well in humans as in mice, it could prevent tens of thousands of second breast cancers. "Unfortunately, breast cancer survivors have a several-times higher risk of developing

cancer in their other breast, compared with healthy women of the same age," explained David Brenner, study leader and Director of Columbia University Medical Center's Center for Radiological Research, "(and) while drugs, such as tamoxifen and aromatase inhibitors, can reduce the risk somewhat … the long-term risks of a second breast cancer in the unaffected breast remain high."

The study, published by *PLoS One,* tested the prophylactic mammary irradiation (PMI) concept using MMTV-PyVT mammary-tumor prone mice. In each mouse, the mammary glands on one side were irradiated with x-rays, while those on the other side were shielded from radiation. The unshielded mammary glands received doses of 0, 4, 8, 12 and 16 Gy in 4-Gy fractions.

Results showed that, in high-risk mammary glands exposed to radiation doses designed for PMI (12 and 16 Gy), the tumor incidence rates decreased by a factor of 2.2 (95% CI: 1.1–5.0) at 12 Gy, and a factor of 3.1 (95% CI: 1.3–8.3) at 16 Gy, respectively, compared with those in the shielded glands that were exposed to very low doses of radiation. This same pattern was seen for PMI-exposed mammary glands relative to zero-dose controls. As such, a moderate dose of radiation reduced the breast cancer risk in the treated side by a factor of approximately 3. "If PMI does, in fact, reduce the incidence of cancer by threefold, as suggested by our results, approximately 100,000 cases of breast cancer could be prevented," Brenner stated.

Research is now planned to test PMI in a clinical trial and, if proven successful in patients, will use PMI as an adjunct to tamoxifen or aromatase inhibitors for women with estrogen receptor-positive tumors and as a standalone therapy for those with estrogen receptor-tumors who do not benefit from drug therapy. In either case, PMI could be performed concurrently with radiotherapy of the affected breast.

"Whether PMI would work for women with *BRACA1* or *BRACA2* mutations, which greatly increase one's risk for breast and/or ovarian cancer, is another story … We don't know that," concluded Brenner, "Our next mouse study will look at the effects of PMI in *BRACA1* mice."

– Written by Ruth Williamson

Sources: Shuryak I, Smilenov LB, Kleiman NJ, Brenner DJ. Potential reduction of contralateral second breast-cancer risks by prophylactic mammary irradiation: validation in a breast-cancer-prone mouse model. *PLoS ONE* 8(12), e85795 (2013); Moderate irradiation of unaffected breast may prevent second cancers: http://newsroom.cumc.columbia.edu/blog/2014/01/23/moderate-doses-of-radiation-therapy-may-prevent-second-breast-cancer

Also featured on www.oncology-central.com

Advances made in uterine fibroid therapy

Uterine fibroids affect 20–40% of women who are of reproductive age. Gonadotropin-releasing hormone agonists are approved as a preoperative therapy for the fibroids; however, they are associated with a number of side effects that limit their use. Esmya® (ulipristal acetate; Gedeon Richter Plc., Budapest, Hungary) is a preoperative therapy that quickly controls uterine bleeding, and reduces anemia and fibroid size. Furthermore, this treatment is said to have fewer side effects than others.

Esmya is a once-daily tablet and, until now, could only be prescribed for up to 3 months to women of reproductive age with moderate-to-severe uterine fibroid symptoms who require a procedure. However, recently, the European Commission has approved its use to retreat patients for an additional 3 months. This approval was obtained following clinical studies demonstrating that a repeated course of Esmya provides continued efficacy and a positive opinion from the Committee for Medicinal Products for Human Use.

A total of 209 patients were recruited in the PEARL III study, which examined the safety and efficacy of a single 3-month open-label treatment with ulipristal acetate 10 mg. When the PEARL III study ended, 132 patients continued to take ulipristal acetate 10 mg in the extension study, which investigated the safety and efficacy of repeated ulipristal acetate 10-mg courses on uterine bleeding, pain, quality of life and myoma size. It is expected that, similar to the 10-mg dose, the 5-mg dose efficacy in the first therapy course will be maintained in the second therapy course.

> "Esmya® has made a significant impact on patients, as it shrinks the fibroids so they are easier to remove, with less blood being lost, making it a safer and shorter operation."

In the Gideon Richter press release, Martin Powell, a consultant gynecologist in Nottingham (UK) comments "Esmya has made a significant impact on patients, as it shrinks the fibroids so they are easier to remove, with less blood being lost, making it a safer and shorter operation. While waiting for surgery, women also have the added benefit of not having heavy bleeding, which can be very debilitating and have a serious impact on quality of life." Furthermore, one individual who was affected by uterine fibroids stated, "I took Esmya for 3 months and felt great – no pain and the heavy bleeding stopped. I had the operation in August 2013 and it went well – I've been absolutely fine since then."

Managing Director of Gedeon Richter Plc., Erik Bogsch, explains "We will now be working with local regulatory agencies to communicate the implications of this label variation to physicians in Europe." Furthermore, additional clinical trials are now in process to determine the sustained safety and efficacy of long-term on/off therapy of uterine fibroids with Esmya.

– Written by Hannah Branch

Source: Gedeon Richter press release: new development in the treatment of uterine fibroids: www.esmya.co.uk

Resistance exercise could reduce risk of developing diabetes in women

A recent study showed that muscle strengthening and toning exercises can help to reduce the risk of diabetes in women.

The study, published in *PLoS Medicine*, prospectively followed-up 99,316, middle-aged and older, women for 8 years from the Nurses' Health Study (2000–2008) and Nurses' Health Study II (2001–2009). None of the women had diabetes at baseline, but, during the 8-year period, 3491 women developed Type 2 diabetes. The likelihood of developing diabetes and the amount of muscle strengthening or conditioning activity (e.g., yoga, stretching and toning) undertaken was found to be directly correlated.

Women who engaged in at least 2.5 h per week of aerobic activity and at least 1 h a week of muscle-strengthening activities had the most substantial risk reduction compared with inactive women. However, even muscle-strengthening activity on its own reduced risk.

"While it was well known that acute effects of muscle-strengthening activity, such as resistance exercise, include improvement in insulin sensitivity of muscle tissue and glycemic control, to what extent long-term engagement in this type of activity would lower risk of diabetes in women has remained unknown," explains Anders Grøntved, from the University of Southern Denmark (Odense, Denmark). "In our study, we show that regular engagement in this type of activity will lower the risk of Type 2 diabetes in women substantially," said Grøntved.

> "...muscle-strengthening activity can serve as an alternative for protection from Type 2 diabetes. We observe that even small amounts of weekly muscle-strengthening activity (<30 min/week) are associated with risk reduction for diabetes."

The influence of resistance training and diabetes risk in men had previously been studied, but until this one, no such study existed that looked at data from women.

Exercise recommendations for women could be affected by the findings. "Our study suggests that, for those women who have difficulty in engaging or adhering to aerobic-type physical activity, muscle-strengthening activity can serve as an alternative for protection from Type 2 diabetes. We observe that even small amounts of weekly muscle-strengthening activity (<30 min/week) are associated with risk reduction for diabetes. Furthermore, women who already engage in aerobic activity will have additional benefit by adding muscle-strengthening activity," Grøntved concluded.

– Written by Laura McGuinness

Source: Grøntved A, Pan A, Mekary RA *et al.* Muscle-strengthening and conditioning activities and risk of Type 2 diabetes: a prospective study in two cohorts of US women. *PLoS Med.* 11(1), e1001587 (2014).

New findings highlight the importance of cervical cancer screening in the over 50s

A study published in *PLoS Medicine* has highlighted the importance of cervical screening in females over the age of 50 years. In particular, the findings reveal that women over 50 years of age who did not attend screenings were six-times more likely to receive a cervical cancer diagnosis in later life.

The research, funded by Cancer Research UK (London, UK) and completed by investigators at Queen Mary University of London (London, UK), involved 1341 females who underwent cervical screening between the ages of 50 and 64. Further data were then collected, identifying the number of these women who were diagnosed between 65 and 83 years old with cervical cancers. Almost all of the women aged 65–83 years, who were diagnosed with cervical cancer in England and Wales between the years 2007 and 2012, were included in the study population.

The results demonstrated women who underwent cervical screening to be at a lower risk of developing cervical cancer in their 80s. This risk was reported to be sixfold higher in women who were not screened after passing their 50th birthday compared with individuals of the same age who had been screened and were given a normal result. Eight cancer cases per 10,000 women were reported over 20 years in those who underwent screening, as opposed to 49 cancers per 10,000 in the unscreened individuals.

"Screening up to the age of 65 greatly reduces the risk of cervical cancer in the following decade, but the protection weakens with time and is substantially weaker 15 years after the last screen. With life expectancy increasing, it's important for countries that stop screening under the age of 60 to look into their screening programs to maximize the number of cervical cancer cases prevented and the number of cervical cancers caught at an early stage," reports Peter Sasieni from Queen Mary University of London.

The women who received abnormal screening results aged 50–64 years but underwent screening on a regular basis presented a risk of 86 per 10,000 women over 20 years. The findings suggest screening during this age range to have an important impact on cervical cancer rates for many years following the examination, even when women reached their 80's the risk of cervical cancer development was still lower in those who underwent testing. Screening every 5 or 3 years appeared to be equally effective.

"These results provide reassurance that there is a real benefit to women over 50 having cervical cancer screening. Screening can pick up abnormal cells in the cervix that could develop into cervical cancer if left alone – removing these cells prevents cancer from developing. Screening is a great way of reducing the risk of cervical cancer, and saves up to 5000 lives a year in the UK. We encourage women to take up cervical screening when invited," concluded Jessica Kirby of Cancer Research UK.

– Written by Elizabeth Webb

Source: Queen Mary University of London press release: www.qmul.ac.uk/media/news/items/smd/119753.html

Also featured on www.oncology-central.com

PROGNOSIS looking good for a possible serum test for preeclampsia

Preeclampsia is the second most common cause of maternal death, affecting one in 20 pregnancies. It can be life-threatening for mother and baby, especially if diagnosed late. PROGNOSIS aims to address the prediction of preeclampsia as an important unmet medical need.

Initial data from the PROGNOSIS study presented at the 18th World Congress on Controversies in Obstetrics, Gynecology & Infertility held in Vienna (Austria) in October 2013, indicated the potential for a serum-based test to improve the conventional diagnostics of preeclampsia (currently based on the clinical parameters hypertension and proteinuria). It is hoped this could allow the easy identification of patients at highest risk, thus improving clinical outcome and healthcare resource allocation.

> "It is possible that if PROGNOSIS yields its anticipated results, there is the potential of using a fully automated test to predict preeclampsia."

PROGNOSIS is a multicenter, prospective, double-blind and noninterventional trial evaluating the short-term prediction of preeclampsia, eclampsia, and hemolysis, elevated liver enzymes and low platelet count syndrome in pregnant women with suspected preeclampsia. The study started enrolling in December 2010 at nine sites in western Europe and was expanded to 31 sites worldwide across Australia, Canada, New Zealand and Latin America in 2012. PROGNOSIS is investigating the correlation between the ratio of two proteins, sFlt-1 and PlGF, in maternal blood, and the risk of developing preeclampsia over the subsequent 4 weeks.

Principal Investigator Harald Zeisler, from the Medical University Vienna (Austria) explained "The PROGNOSIS study will expand the use of these powerful markers for preeclampsia from the very good performance for aid in diagnosis towards the area of prediction and early risk stratification. We hope that early identification of women at high risk of developing preeclampsia will allow healthcare professionals to prevent the most serious effects of the disease, and avoid unnecessary expenditure by healthcare systems on excessive medical treatment or unnecessary hospital admission prompted by inadvertently positive diagnoses based on current standard of clinical practice."

It was back in 2010 that Roche (Basel, Switzerland) introduced Elecsys® to the UK market, which provides healthcare professionals with a reliable tool for the diagnosis of preeclampsia. It is possible that if PROGNOSIS yields its anticipated results, there is the potential of using a fully automated test to predict preeclampsia. A predictive test would enable healthcare professionals to focus on patients at highest need of appropriate and timely clinical treatment, and those patients who are identified as unlikely to develop the disease could be safely discharged from hospital.

Interim analysis of the data from the first 500 patients included in the study have demonstrated promising results, with an approximately 20% prevalence of preeclampsia in the target population. Full results are expected to be reported in 2014.

– Written by Michael Dowdall

Source: Roche press release: PROGNOSIS study to determine whether serum test predicts preeclampsia: www.roche.co.uk/portal/uk/2013_press_releases?siteUuid=re7208002&paf_gear_id=41800051&pageId=re7734007&synergyaction=show&paf_dm=full&nodeId=1415-e8cf5f0f5bfb11e3b54defe0692339e3&currentPage=0

In brief...

An Y, Sun Z, Zhang Y, Liu B, Guan Y, Lu M. The use of berberine for women with polycystic ovary syndrome undergoing IVF treatment. **Clin. Endocrinol. (Oxf.)** ***80(3), 425–431 (2014).***

Reduced insulin sensitivity has been reported to adversely affect IVF outcomes in patients with polycytsic ovary syndrome. It has previously been suggested that the drug berberine is an effective insulin sensitizer with equivalent efficacy to metformin. In this study, the team have evaluated the clinical, metabolic and endocrine effects of berberine compared with metformin, in women with polycytsic ovary syndrome scheduled for IVF treatment, in order to investigate the potential advantages to the IVF procedure. In total, 150 infertile women were randomized to receive berberine, metformin or placebo tablets for 3 months before ovarian stimulation. It was observed that 3-month treatment with berberine or metformin before IVF reduced the incidence of severe ovarian hyperstimulation syndrome and increased the pregnancy rate in the subjects. Compared with berbarine, metformin was associated with increased live birth rates and fewer gastrointestinal adverse events in women with polycytsic ovary syndrome.

Killeen JL, Dye T, Grace C, Hiraoka M. Improved abnormal pap smear triage using cervical cancer biomarkers. **J. Low. Genit. Tract Dis.** ***18(1), 1–7 (2014).***

The current standard cervical smear screening procedure has led to a pronounced reduction in cases of invasive cervical cancer. However, the low specificity of high-risk human papillomavirus (HPV) triage means that many women undergo additional procedures (e.g., repeat cervical smear tests, colposcopy and cervical biopsies) unnecessarily, as significant precursor lesions are rarely found. In this study, the team investigated the potential use of more specific cervical cancer biomarkers (p16 and Ki-67) as a more effective triage tool than high-risk HPV screening. The team performed p16/Ki-67 immunostaining on additional slides prepared from 515 women with abnormal cervical smear results. High-risk HPV typing was also performed on all samples. The results from immunostaining and high-risk HPV testing were then compared for diagnostic accuracy for the detection of biopsy-proven cervical intraepithelial neoplasia 2/3. The sensitivity/specificity of high-risk HPV and p16/Ki-67 for the detection of cervical intraepithelial neoplasia 2/3 was 89.29/14.94 and 96.43/60.92%, respectively, making diagnostic accuracy significantly higher for p16/Ki-67 than for high-risk HPV. The use of biomarker triage may significantly reduce healthcare costs, without affecting the quality of cervical cancer detection.

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of women's health. If you have newsworthy information, please contact:
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