Accepted Abstracts

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Psychological intervention in women with non-metastatic breast cancer: Cochrane review

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As survival rates have improved with advances in medical care, the importance of psychiatric interventions designed to assist cancer patients in dealing with diagnosis and treatment has increased. There are four major categories on interventions described most frequently in the literature. These are educational techniques, behavioural training, individual psychotherapy, and group interventions. We have some knowledge of the effectiveness of psychological interventions on psychiatric outcomes such as depression and anxiety. We know much less about cognitive impairment, employment, quality of life and relationships. Even where we have evidence, it is mostly of only moderate quality, is most often only for breast cancer and focuses almost exclusively on the early phase of survivorship. There is little research into the needs of minority groups and certain cancers, such as lung cancer and the less common cancers. Most study samples are simply too small to give robust results. A wide variety of measures have been used with little consistency between studies making the combination of data across studies problematic. Research may be needed to work out how to implement these interventions in everyday practice. There has been a substantial amount of research describing many of the psychological interventions employed for the cancer survivors. However, the quality of the evidence is often poor, and some topics have been little examined. We need data and robust testing of psychological interventions in clinical trials obtained from well-designed, large-scale studies.

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Impact of colorectal cancer diagnosis and treatment on health-related quality of life among older Ugandans: A population-based, case-control study

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Background: Data on health-related quality of life (HRQoL) changes among Americans aged ≥65 following colorectal cancer (CRC) diagnosis and treatment are limited. This study compared HRQoL changes among CRC patients across stages from before to after diagnosis with matched noncancer controls.

Methods: This population-based study used the Surveillance, Epidemiology, and End Results Medicare Health Outcomes Survey (MHOS) data set (2011-2015). Medicare Advantage beneficiaries diagnosed with CRC between their baseline and follow-up MHOS (n = 349) were matched to noncancer controls (n = 1745) using propensity scores. Mixed-effects analysis of covariance models estimated changes in HRQoL (measured by the Medical Outcomes Study Short Form-36/ Veterans RAND 12-item Survey) and the ability to perform 6 activities of daily living (ADLs) between baseline and follow-up. Logistic regression models estimated odds ratios for ADL impairments and major depressive disorder (MDD) risk.

Results: Mean time between CRC diagnosis and follow-up MHOS was 12.3 ± 9.8 months. Compared with controls, CRC patients had significantly lower scores in all physical and mental health domains at follow-up. The greatest decrements were observed in physical health and were largely driven by declines in the 6 months postdiagnosis and in stage III and IV patients. At follow-up, CRC patients had greater overall ADL impairment and difficulty with dressing, eating, and getting in/out of chairs. CRC patients, particularly stage IV patients, had greater odds of being at risk for MDD relative to controls.

Conclusions: This study further underscores the adverse effects of CRC on physical health and the need to support older Ugandas' basic self-care needs, with attention to later-stage patients' increased debility.

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The Soy – Breast Cancer Question

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Breast cancer remains a serious world-wide problem. It continues to be the leading form of cancer in women both in North America and in developing countries. More than 200,000 women are diagnosed with breast cancer each year in the U.S. alone. The mainstays of treatment continue to be surgery, radiation, chemo- and endocrine therapies, although the anti-cancer potencies of several natural agents have entered clinical trials, including herbal supplements, vitamins, sponge and coral derivatives, and a range of dietary products. Notably, many are used by women with a recent diagnosis of breast cancer without their physician's knowledge. Although none has proven curative, dietary agents are seen by many as safe, low-risk alternatives to the more potent chemotherapeutic drugs currently used against breast cancer. One example is genistein, a soy-derived phytoestrogen which is known to have cytoprotective as well as cytotoxic effects on breast cancer cells. It is estimated that over one million women consume phytoestrogens worldwide even though questions regarding their effects on breast cancer risk, progression, and/or treatment responses are largely unsettled. In our studies three different human breast cancer cell sublines were established using long-term, low-dose exposure protocols. This was accomplished by passing a single parental cell line in media supplemented with genistein, estradiol, or tamoxifen as well as unsupplemented media used for controls, followed by maintenance in parallel for a period of two years. The resulting sublines were characterized for changes in DNA- and ligand-binding; target gene activation; estrogen receptor expression, cell morphology, growth and survival; as well as ploidy; cell cycle distribution, and responses to treatment with the anti-cancer agent paclitaxel.

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Home-based exercise to manage aromatase inhibitor (AI) associated arthralgia in women diagnosed with early breast cancer1

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Breast cancer (BC) is largely a disease of aging, with most new cases diagnosed in women who are postmenopausal. In the 70-80% of these women whose BC tumors are hormone receptor positive (HR+), national guidelines call for adjuvant endocrine treatment that includes an aromatase inhibitor (AI). Most women on an AI (74%) report joint pain, stiffness or achiness (arthralgia), and for many women these symptoms are moderate to severe. As AIs are prescribed for 5 years and potentially as many as 10 years, moderate-to-severe AI-arthralgia can be a factor in AI discontinuation and suboptimal adherence, and compromises quality of life in survivorship. This study investigated whether a home-based walking program (adapted from the Arthritis Foundations' Walk With Ease program) could provide a safe and effective approach to managing AI-Arthralgia. A randomized controlled trial compared women who were asked to walk at least 150 minutes per week over a 6-week period (Intervention) with Wait List Control. Our final sample (N=62) had a mean age of 64 years and 74% are white. At six weeks, Intervention participants reported significantly increased walking minutes/week ($p<0.01$), reduced stiffness ($p<0.05$), fewer limitations in activities of daily living (ADL) ($p<0.01$), and increased confidence in managing their joint symptoms ($p<0.01$). At 6 months post-intervention, stiffness and ADL benefits had been maintained, although walking minutes/week had decreased. This study contributes to the growing evidence that exercise can be a safe and effective alternative or complement to medications for AI-arthralgia management.

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Colorectal cancer subtypes: Translation to routine clinical pathology

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Colorectal cancer (CR) is the second most common cause of cancer death in Uganda. Although outcomes have improved, it is clear that from a genomic standpoint CR is not one disease, but a heterogeneous group of malignancies that arise within one organ. Given that different subtypes have different outcomes, the ability to subtype tumours in the clinic would be highly favourable, enabling optimal treatment for individual patients. In 2015, a consortium proposed four consensus subtypes for CRC (MSI immune, canonical, metabolic, and mesenchymal) based on six classifications systems reported to have prognostic value. However, genomic assessment of tumours is not readily translated into routine pathology with a need for standardisation and reproducibility of assessment. Immunohistochemistry is widely used in routine pathology, and would present a more readily translatable method for subtyping CRC tumours. Therefore, the literature was reviewed to characterise the genomic and phenotypic features associated with each subtype, with the aim of enabling subtyping of CRC to be taken forward into routine clinical practice.

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Phase II trial of the PI3 kinase inhibitor buparlisib (BKM-120) with or without enzalutamide in men with metastatic castration resistant prostate cancer

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Background: Phosphatidylinositol-3-kinase (PI3K) and androgen receptor pathway activation is common in metastatic castration resistant prostate cancer (mCRPC). Buparlisib is an oral, pan-class I PI3 kinase inhibitor.

Methods: This was a multisite single arm phase II trial of buparlisib 100 mg ± enzalutamide daily in men with mCRPC whose disease progressed on or who were not candidates for docetaxel. The primary end-point was the rate of radiographic/clinical progression-free survival (PFS) at 6 months.

Results: Thirty men were accrued: 67% post-docetaxel; median prostate specific antigen (PSA) was 70 ng/dl, 83% had ≥4 prior therapies for mCRPC; 43% received concurrent enzalutamide. The final 6 month PFS rate was estimated to be 10% (95% confidence interval 2.5–23.6%). Median PFS was 1.9 months and was 3.5 months with concurrent enzalutamide. Median overall survival was 10.6 months. Concurrent enzalutamide led to a five-fold reduction in buparlisib concentrations. PSA declines were observed in 23%; no patients achieved a ≥50% decline, and no radiographic responses were observed. Severe adverse events occurred in four men including respiratory infection and multi-organ failure, urinary tract obstruction, confusion and one seizure in the setting of a new central nervous system (CNS) metastasis. Grade III adverse events were seen in 43% of patients; common toxicities included grade I–II weight loss, diarrhoea, nausea, fatigue, anorexia, rash, hyperglycemia and anxiety/mood disorders.

Conclusions: Buparlisib did not demonstrate significant activity in men with mCRPC, suggesting that PI3K inhibition is not sufficient to reverse resistant mCRPC progression. Future studies of PI3K pathway inhibitors with concurrent enzalutamide should develop optimal dosing and focus on selected patients more likely to benefit.

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Distinct immunologic changes *in vivo* following combination versus individual PD-1 or CTLA-4 checkpoint blockade in human cancer

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Therapies targeting T cell immune checkpoints such as CTLA4 and PD1/PDL1 axis have shown considerable promise in the therapy of human cancer. Combination therapy with dual immune checkpoint blockade (ICB) was recently shown to be highly active in melanoma. While signaling via both PD1 and CTLA4 is known to converge downstream and dampen T cell function, data comparing *in vivo* effects of blockade of these immune checkpoints either alone or in combination *in vivo* in humans are limited. Here we have analyzed paired pre/post therapy samples from patients treated either anti-CTLA4 (n = 5) or anti-PD1 (n = 6) alone, or a combination of anti-CTLA4 and anti-PD1 (n = 8), using several methodologies including multi-parameter flow cytometry, single-cell mass-cytometry (CyTOF), Luminex and analysis of transcriptome of purified immune cells with exon-level arrays. We show that blockade of CTLA4, PD1 or combination blockade leads to distinct immunologic, genomic and cytokine signatures *in vivo*. CTLA4 blockade leads to a prominent proliferation signature *in vivo*, manifest as an increase in Ki-67 expression in a subset of T cells with transitional memory phenotype. PD1 blockade does not induce this phenotype and instead leads to marked changes in T cells expressing NK and cytolysis associated genes, as exemplified by Granzyme+ T cells. Combination blockade leads to non-overlapping changes in gene expression including proliferation-associated and chemokine genes and leads to an increase in both Ki67+and Granzyme+ T cells. Overall, therapy-induced changes are more prominent in T cells than in monocytes include also involve non-overlapping changes in several alternatively spliced transcripts and non-coding RNAs. Each of the ICB therapies also leads to a distinct cytokine profile with differential effects on systemic levels of sIL2R and IL1a. Changes seen in the peripheral blood T cells can also be seen in the tumor infiltrating lymphocytes. Combination therapy leads to an increase in interferon-gamma producing T cells in both circulation as well as tumor bed. PD1 expression is higher on tumor infiltrating T cells when compared to T cells in circulation. Importantly, PD1 receptor occupancy following anti-PD1 therapy may be incomplete in the tumor infiltrating T cells even in the setting of complete receptor occupancy in circulating T cells. These data demonstrate that blockade of PD1, CTLA4 alone or in combination have distinct immunologic effects *in vivo* and each strategy serves as a unique immune-therapeutic. Improved understanding of the *in vivo* effects of ICB is needed for rational development of future immune-based combinations against cancer.

Awareness about Early Detection Methods, Symptoms and Risk Factors towards Breast and Cervical Cancer among the Female Students

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The study was conducted to ensure knowledge, attitude, awareness about breast and cervical cancer among the female students of Makerere University. This study was carried out from July to September, 2016 among the participants of university female halls, different female hostels and different faculty of the university by using a validated questionnaire which was developed for this study. A total 250 female students, at the age of (18 - 26) years were participated. Collected information was analyzed using SPSS, Graph-pad Prism and MS Excel. The results showed that about 87.6% participants were undergraduate. Most of them come from village (45.6%) and city (36.0%). In case of food intake patterns, it was observed that 35.6% participants eat chips, soft drinks, popcorn everyday; 40.4% eat meat regularly; 24% eat sugar everyday; 27.6% eat fruits and vegetables every day. Among them, 55.6% girls maintained daily 1 hour physical activity; 37.2% did exercise rarely; 34.8% participants rarely do strenuous exercise. About 84.4% respondents have not any family history of cancer; 6% participants have sister or mother having breast tumor and 7.2% have at least more than one close relative who have cancer. Among the participants, only 0.8% drank alcohol; 1.2% have addiction of smoking cigarette; 15.6% girls wear tight bra; 3.6% have benign breast disease and 2.8% participants have attended in breast or cervical cancer screening programs. The moderate numbers of girls have breast cancer screening practice. Among them, only 28.8% participants have ever heard about BSE (Breast self-examination) and 40.4% have not any knowledge about breast cancer treatment. About 50.8% respondents don't have any knowledge about cervical cancer treatment. The village people are the most risky group. About 17.02% girls recognized weakened immune system as a risk factor of cervical cancer. It can be concluded that, knowledge of participants regarding breast and cervical cancer is poor. Targeted education should be implemented to improve the knowledge of respondents about early detection methods and symptoms of breast and cervical cancer.

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Distinct immunologic changes *in vivo* following combination versus individual PD-1 or CTLA-4 checkpoint blockade in human cancer

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Therapies targeting T cell immune checkpoints such as CTLA4 and PD1/PDL1 axis have shown considerable promise in the therapy of human cancer. Combination therapy with dual immune checkpoint blockade (ICB) was recently shown to be highly active in melanoma. While signaling via both PD1 and CTLA4 is known to converge downstream and dampen T cell function, data comparing *in vivo* effects of blockade of these immune checkpoints either alone or in combination *in vivo* in humans are limited. Here we have analyzed paired pre/post therapy samples from patients treated either anti-CTLA4 (n = 5) or anti-PD1 (n = 6) alone, or a combination of anti-CTLA4 and anti-PD1 (n = 8), using several methodologies including multi-parameter flow cytometry, single-cell mass-cytometry (CyTOF), Luminex and analysis of transcriptome of purified immune cells with exon-level arrays. We show that blockade of CTLA4, PD1 or combination blockade leads to distinct immunologic, genomic and cytokine signatures *in vivo*. CTLA4 blockade leads to a prominent proliferation signature *in vivo*, manifest as an increase in Ki-67 expression in a subset of T cells with transitional memory phenotype. PD1 blockade does not induce this phenotype and instead leads to marked changes in T cells expressing NK and cytolysis associated genes, as exemplified by Granzyme+ T cells. Combination blockade leads to non-overlapping changes in gene expression including proliferation-associated and chemokine genes and leads to an increase in both Ki67+and Granzyme+ T cells. Overall, therapy-induced changes are more prominent in T cells than in monocytes include also involve non-overlapping changes in several alternatively spliced transcripts and non-coding RNAs. Each of the ICB therapies also leads to a distinct cytokine profile with differential effects on systemic levels of sIL2R and IL1a. Changes seen in the peripheral blood T cells can also be seen in the tumor infiltrating lymphocytes. Combination therapy leads to an increase in interferon-gamma producing T cells in both circulation as well as tumor bed. PD1 expression is higher on tumor infiltrating T cells when compared to T cells in circulation. Importantly, PD1 receptor occupancy following anti-PD1 therapy may be incomplete in the tumor infiltrating T cells even in the setting of complete receptor occupancy in circulating T cells. These data demonstrate that blockade of PD1, CTLA4 alone or in combination have distinct immunologic effects *in vivo* and each strategy serves as a unique immune-therapeutic. Improved understanding of the *in vivo* effects of ICB is needed for rational development of future immune-based combinations against cancer.

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Mutagenic and Cytotoxic Effects of Doxorubicin (Adriamycin) and Epeirubicin, Common Anthracycline DNA II Topoisomerase Inhibitors Used Against Breast Cancer, in Prokaryotic and Eukaryotic Cells

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For more than 40 years, anthracyclines have represented one of the most commonly used anticancer drugs. Doxorubicin and epirubicin are the morst common chemicals used against breast cancer, It is known that anthracyclines interact with the DNA double helix in a variety of very complex manners, which include intercalation of doxorubicin into the DNA duplex, formation of formaldehyde-mediated DNA crosslinks (primarily between neighboring guanines), and the catalytic inhibition of DNA topoisomerse II. Numerous studies in our lab have shown that four anthracyclines (daunorubicin, idarubicin, doxorubicin, and epirubicin) can induce DNA base excision repair and O6 alkylguanine DNA repair alkyltransferase- dependent base-substitution events and frameshift mutaions in the bacterium Salmonella typhimurium. More recent studies evaluated the recombinogenic potential of anthracyclines in a eukaryotic unicellular organism Saccharomyces cerevisiae. In the yeast deletion (DEL) assay, recombination is induced by the formation of DNA strand breaks, which are a substrate for initiation of genetic repair in this organism. Using the DEL assay, our lab has examined the role of DNA recombination pathways in the recognition and removal of anthracycline-induced DNA adducts. Specifically, doxorubicin (49.1 fold) and epirubicin (279 fold) tested positive in this assay. Our next step is to examine the pre-carcinogenic anthracycline-dependent events in mammals.

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