BMP4 inhibits the proliferation of breast cancer cells and induces an MMP-dependent migratory phenotype in MDA-MB-231 cells in 3D environment

Background: Bone morphogenetic protein 4 (BMP4) belongs to the transforming growth factor β (TGF-β) family of proteins. BMPs regulate cell proliferation, differentiation and motility, and have also been reported to be involved in cancer pathogenesis. We have previously shown that BMP4 reduces breast cancer cell proliferation through G1 cell cycle arrest and simultaneously induces migration in a subset of these cell lines. Here we examined the effects of BMP4 in a more physiological environment, in a 3D culture system.Methods: We used two different 3D culture systems; Matrigel, a basement membrane extract from mouse sarcoma cells, and a synthetic polyethylene glycol (PEG) gel. AlamarBlue reagent was used for cell proliferation measurements and immunofluorescence was used to determine cell polarity. Expression of cell cycle regulators was examined by Western blot and matrix metalloproteinase (MMP) expression by qRT-PCR. Results: The MCF-10A normal breast epithelial cells formed round acini with correct apicobasal localization of α6 integrin in Matrigel whereas irregular structures were seen in PEG gel. The two 3D matrices also supported dissimilar morphology for the breast cancer cells. In PEG gel, BMP4 inhibited the growth of MCF-10A and the three breast cancer cell lines examined, thus closely resembling the 2D culture conditions, but in Matrigel, no growth inhibition was observed in MDA-MB-231 and MDA-MB-361 cells. Furthermore, BMP4 induced the expression of the cell cycle inhibitor p21 both in 2D and 3D culture, thereby partly explaining the growth arrest. Interestingly, MDA-MB-231 cells formed large branching, stellate structures in response to BMP4 treatment in Matrigel, suggestive of increased cell migration or invasion. This effect was reversed by Batimastat, a broad-spectrum MMP inhibitor, and subsequent analyses showed BMP4 to induce the expression of MMP3 and MMP14, that are thus likely to be responsible for the stellate phenotype. Conclusions: Taken together, our results show that Matrigel provides a more physiological environment for breast epithelial cells than PEG gel. Moreover, BMP4 partly recapitulates in 3D culture the growth suppressive abilities previously seen in 2D culture and induces an MMP-dependent migratory phenotype in MDA-MB-231 cells.

General information

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Contributors: Ampuja, M., Jokimäki, R., Juuti-Uusitalo, K., Rodriguez-Martinez, A., Alarmo, E. L., Kallioniemi, A.
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Research output: Contribution to journal › Article › Scientific › peer-review

Chernobyl fallout and cancer incidence in Finland 1988-2007

Twenty-five years have passed since the Chernobyl accident, but its health consequences remain to be well established. Finland was one of the most heavily affected countries by the radioactive fallout outside the former Soviet Union. We analyzed the relation of the estimated external radiation exposure from the fallout to cancer incidence in Finland in 1988-2007. The study cohort comprised all ~3.8 million Finns who had lived in the same dwelling for 12 months following the accident (May 1986-April 1987). Radiation exposure was estimated using data from an extensive mobile dose rate survey. Cancer incidence data were obtained for the cohort divided into four exposure categories (the lowest with the first-year committed dose

General information

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Organisations: Prostate cancer research center (PCRC), International Agency for Research on Cancer, Univ of Oulu, National Public Health Institute, STUK - Radiation and Nuclear Safety Authority, Finnish Cancer Registry
Contributors: Auvinen, A., Seppä, K., Pasanen, K., Kurttio, P., Patama, T., Pukkala, E., Heinävaara, S., Arvela, H., Verkasalo, P., Hakulinen, T.

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Research output: Contribution to journal › Article › Scientific › peer-review

FRα: une cible pour la thérapie photodynamique prophylactique des métastases péritonéales ovariennes?
Partly due to delays in its diagnosis, ovarian cancer's prognosis remains dire after primary therapy. Treatment consists in complete cytoreductive surgery and platinum-based chemotherapy. Recurrence rates are disappointingly high, as 60 % of women with advanced epithelial ovarian cancer considered in remission will develop recurrent disease within five years. Special attention to undetected peritoneal metastasis and residual tumorous cells during surgery is necessary as they are the main predictors of recurrences. Targeted therapies aim to bring chemotherapy, radiotherapy and selective tumor photosensitizer (PS) agents to the targeted cell and its tumoral microenvironment. Folate receptor α (FRα) shows promising prospects in targeting ovarian cancerous cells. Indeed, with good specificity and frequent overexpression in ovarian cancer, FRα is a recurrent topic in recent publications. The aim of this review is to present FRα and the reasons that make it an ideal targeting ligand for ovarian carcinoma therapy. Prophylactic photodynamic therapy (PPDT) using new generation FRα-coupled agents combined with complete cytoreductive surgery could allow for a significant decrease in recurrence rates. Preclinical trials are being run in order to allowfor human clinical applications.

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Organisations: Frontier Photonics, Lille University Hospital - CHRU, Université de Lorraine
Contributors: Azaïs, H., Moussaron, A., Bach, S. K., Bassil, A., Betrouni, N., Frochot, C., Collinet, P., Mordon, S.
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Original language: French
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Keywords: Folate receptor α, Ovarian cancer, Peritoneal carcinomatosis, Prophylactic photodynamic therapy, Targeted therapy
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Research output: Contribution to journal › Review Article › Scientific › peer-review

Bcl-2 associated athanogene 5 (Bag5) is overexpressed in prostate cancer and inhibits ER-stress induced apoptosis

Background: The Bag (Bcl-2 associated athanogene) family of proteins consists of 6 members sharing a common, single-copied Bag domain through which they interact with the molecular chaperone Hsp70. Bag5 represents an exception in the Bag family since it consists of 5 Bag domains covering the whole protein. Bag proteins like Bag1 and Bag3 have been implicated in tumor growth and survival but it is not known whether Bag5 also exhibits this function.Methods: Bag5 mRNA and protein expression levels were investigated in prostate cancer patient samples using real-time PCR and immunoblot analyses. In addition immunohistological studies were carried out to determine the expression of Bag5 in tissue arrays. Analysis of Bag5 gene expression was carried out using one-way ANOVA and Bonferroni's Multiple Comparison test. The mean values of the Bag5 stained cells in the tissue array was analyzed by Mann-Whitney test. Functional studies of the role of Bag5 in prostate cancer cell lines was performed using overexpression and RNA interference analyses.Results: Our results show that Bag5 is overexpressed in malignant prostate tissue compared to benign samples. In addition we could show that Bag5 levels are increased following endoplasmic reticulum (ER)-stress induction, and Bag5 relocates from the cytoplasm to the ER during this process. We also demonstrate that Bag5 interacts with the ER-resident chaperone GRP78/BiP and enhances its ATPase activity. Bag5 overexpression in 22Rv.1 prostate cancer cells inhibited ER-stress induced apoptosis in the unfolded protein response by suppressing PERK-eIF2-ATF4 activity while enhancing the IRE1-Xbp1 axis of this pathway. Cells expressing high levels of Bag5 showed reduced sensitivity to apoptosis induced by different agents while Bag5 downregulation resulted in increased stress-induced cell death.Conclusions: We have therefore shown that Bag5 is overexpressed in prostate cancer and plays a role in ER-stress induced apoptosis. Furthermore we have identified GRP78/BiP as a novel interaction partner of Bag5.

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Organisations: Prostate cancer research center (PCRC), Karlsruhe Institute of Technology, Campus North, Innsbruck Medical University, Tampere University Hospital
Contributors: Bruchmann, A., Roller, C., Walther, T. V., Schäfer, G., Lehmusvaara, S., Visakorpi, T., Klocker, H., Cato, A. C. B., Maddalo, D.
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Research output: Contribution to journal › Article › Scientific › peer-review

Changes in circulating microRNA levels associated with prostate cancer

BACKGROUND: The aim of this study was to investigate the hypothesis that changes in circulating microRNAs (miRs) represent potentially useful biomarkers for the diagnosis, staging and prediction of outcome in prostate cancer. METHODS: Real-time polymerase chain reaction analysis of 742 miRs was performed using plasma-derived circulating microvesicles of 78 prostate cancer patients and 28 normal control individuals to identify differentially quantified miRs. RESULTS: A total of 12 miRs were differentially quantified in prostate cancer patients compared with controls, including 9 in patients without metastases. In all, 11 miRs were present in significantly greater amounts in prostate cancer patients with metastases compared with those without metastases. The association of miR-141 and miR-375 with metastatic prostate cancer was confirmed using serum-derived exosomes and microvesicles in a separate cohort of patients with recurrent or non-recurrent disease following radical prostatectomy. An analysis of five selected miRs in urine samples found that miR-107 and miR-574-3p were quantified at significantly higher concentrations in the urine of men with prostate cancer compared with controls. CONCLUSION: These observations suggest that changes in miR concentration in prostate cancer patients may be identified by analysing various body fluids. Moreover, circulating miRs may be used to diagnose and stage prostate cancer.

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Organisations: Prostate cancer research center (PCRC), University of Oxford, Research and Development Division, University of Sheffield, Visiting Graduate Student in Department of Urban Design and Planning, University of Washington, Seattle, USA 1.1.2012-15.6.2012 (12.9.2011 alkaen), School of Management (JKK)
Contributors: Bryant, R. J., Pawlowski, T., Catto, J. W. F., Marsden, G., Vessella, R. L., Rhees, B., Kuslich, C., Visakorpi, T., Hamdy, F. C.
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RE: Prostate-specific antigen screening trials and prostate cancer deaths: The androgen deprivation connection

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Organisations: Prostate cancer research center (PCRC), University of Gothenburg, Erasmus University Medical Center, School of Management (JKK)
Contributors: Carlsson, S., Roobol, M. J., Schröder, F. H., Hugosson, J., Auvinen, A.
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Research output: Contribution to journal › Letter › Scientific › peer-review

Thérapie photodynamique et carcinomes urothéliaux
Purpose. Photodynamic therapy (PDT) is an innovative therapeutic modality in urologic oncology. Material and methods. We reviewed the current literature on principles and modalities of PDT in urothelial and penile oncology. Results. PDT has been tested for the treatment recurrent superficial bladder tumors and in situ carcinoma. Carcinologic efficacy has been

observed with first generation photosensitizer. The lack of selectivity for tumoral cells was responsible of serious adverse events. Development of selective photosensitizers has reduced the importance of side effects. Data concerning PDT for upper urinary tract and urethra carcinoma are still limited. Conclusion. First PDT clinical applications in urothelial oncology have shown some effectiveness at the cost of significant morbidity. The development of selective photosensitizers should help to reduce side effects.

General information

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Organisations: Frontier Photonics, Lille University Hospital - CHRU, Univ Lille Nord de France, Université Nord de France
Contributors: Colin, P., Estevez, J. P., Betrouni, N., Nevoux, P., Puech, P., Leroy, X., Biserte, J., Villers, A., Mordon, S.
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Keywords: Bladder, Photodynamic therapy, Upper urinary tract, Urethra, Urothelial carcinoma
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Source ID: 79960511654
Research output: Contribution to journal › Review Article › Scientific › peer-review

Genome-wide linkage scan for prostate cancer susceptibility in Finland: Evidence for a novel locus on 2q37.3 and confirmation of signal on 17q21-q22

Genome-wide linkage studies have been used to localize rare and highly penetrant prostate cancer (PRCA) susceptibility genes. Linkage studies performed in different ethnic backgrounds and populations have been somewhat disparate, resulting in multiple, often irreproducible signals because of genetic heterogeneity and high sporadic background of the disease. Our first genome-wide linkage study and subsequent fine-mapping study of Finnish hereditary prostate cancer (HPC) families gave evidence of linkage to one region. Here, we conducted subsequent scans with microsatellites and SNPs in a total of 69 Finnish HPC families. GENEHUNTER-PLUS was used for parametric and nonparametric analyses. Our microsatellite genome-wide linkage study provided evidence of linkage to 17q12-q23, with a heterogeneity LOD (HLOD) score of 3.14 in a total of 54 of the 69 families. Genome-wide SNP analysis of 59 of the 69 families gave a highest HLOD score of 3.40 at 2q37.3 under a dominant high penetrance model. Analyzing all 69 families by combining microsatellite and SNP maps also yielded HLOD scores of > 3.3 in two regions (2q37.3 and 17q12-q21.3). These significant linkage peaks on chromosome 2 and 17 confirm previous linkage evidence of a locus on 17q from other populations and provide a basis for continued research into genetic factors involved in PRCA. Fine-mapping analysis of these regions is ongoing and candidate genes at linked loci are currently under analysis.

General information

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Organisations: Prostate cancer research center (PCRC), National Human Genome Research Institute, Tampere University Hospital, Fox Chase Cancer Center, Johns Hopkins Bloomberg School of Public Health
Contributors: Cropp, C. D., Simpson, C. L., Wahlfors, T., Ha, N., George, A., Jones, M. S., Harper, U., Ponciano-Jackson, D., Green, T. A., Tammela, T. L. J., Bailey-Wilson, J., Schleutker, J.
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Research output: Contribution to journal › Article › Scientific › peer-review

Guggulsterone sensitizes glioblastoma cells to Sonic hedgehog inhibitor SANT-1 induced apoptosis in a Ras/NFκB dependent manner

Since Shh pathway effector, Gli1, is overexpressed in gliomas, we investigated the effect of novel Shh inhibitor SANT-1 on glioma cell viability. Though SANT-1 failed to induce apoptosis, it reduced proliferation of glioma stem-like cells. Apart from canonical Shh cascade, Gli1 is also induced by non-canonical pathways including NFκB. Therefore, a combinatorial strategy with Ras/NFκB inhibitor, Guggulsterone, was employed to enhance effectiveness of SANT-1. Guggulsterone inhibited Ras and NFκB activity and sensitized cells to SANT-1 induced apoptosis via intrinsic apoptotic mechanism. Inhibition of either Ras or NFκB activity was sufficient to sensitize cells to SANT-1. Guggulsterone induced ERK activation also contributed to Caspase-9 activation. Since SANT-1 and Guggulsterone differentially target stem-like and non-stem glioma cells respectively, this combination warrants investigation as an effective anti-glioma therapy.

General information

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Organisations: Computational Science X (CompX), National Brain Research Centre, National Cancer Institute
Contributors: Dixit, D., Ghildiyal, R., Anto, N. P., Ghosh, S., Sharma, V., Sen, E.
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Research output: Contribution to journal › Article › Scientific › peer-review

Inhibition of Casein kinase-2 induces p53-dependent cell cycle arrest and sensitizes glioblastoma cells to tumor necrosis factor (TNFα)-induced apoptosis through SIRT1 inhibition

Glioblastoma multiforme (GBM) are resistant to TNFα-induced apoptosis and blockade of TNFα-induced NF-κB activation sensitizes glioma cells to apoptosis. As Casein kinase-2 (CK2) induces aberrant NF-κB activation and as we observed elevated CK2 levels in GBM tumors, we investigated the potential of CK2 inhibitors (CK2-Is)-DRB and Apigenin in sensitizing glioma cells to TNFα-induced apoptosis. CK2-Is and CK2 small interfering RNA (siRNA) reduced glioma cell viability, inhibited TNFα-mediated NF-κB activation, and sensitized cell to TNFα-induced apoptosis. Importantly, CK2-Is activated p53 function in wild-type but not in p53 mutant cells. Activation of p53 function involved its increased transcriptional activation, DNA-binding ability, increased expression of p53 target genes associated with cell cycle progression and apoptosis. Moreover, CK2-Is decreased telomerase activity and increased senescence in a p53-

dependent manner. Apoptotic gene profiling indicated that CK2-Is differentially affect p53 and TNFα targets in p53 wild-type and mutant glioma cells. CK2-I decreased MDM2-p53 association and p53 ubiquitination to enhance p53 levels. Interestingly, CK2-Is downregulated SIRT1 activity and over-expression of SIRT1 decreased p53 transcriptional activity and rescued cells from CK2-I-induced apoptosis. This ability of CK2-Is to sensitize glioma to TNFα-induced death via multiple mechanisms involving abrogation of NF-κB activation, reactivation of wild-type p53 function and SIRT1 inhibition warrants investigation.

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Contributors: Dixit, D., Sharma, V., Ghosh, S., Mehta, V. S., Sen, E.
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Source ID: 84857852626
Research output: Contribution to journal › Article › Scientific › peer-review

Responder analysis of the effects of denosumab on bone mineral density in men receiving androgen deprivation therapy for prostate cancer
Background: Denosumab, a fully human monoclonal antibody against RANK ligand, increased bone mineral density (BMD) and reduced fracture risk vs placebo in a phase 3 trial in men with prostate cancer on androgen deprivation therapy (ADT). The present analysis of this study evaluated BMD changes after 36 months in responder subgroups and in individual patients for three key skeletal sites (lumbar spine (LS), femoral neck (FN) and total hip (TH)) and the distal radius. Methods: Men with nonmetastatic prostate cancer receiving ADT were treated with subcutaneous denosumab 60 mg (n=734) or placebo (n=734) every 6 months for up to 36 months in a phase 3, randomized, double-blind study. Patients were instructed to take supplemental calcium and vitamin D. For this BMD responder analysis, the primary outcome measure was the percentage change in BMD from baseline to month 36 at the LS, FN and TH as measured by dual-energy X-ray absorptiometry. BMD at the distal 1/3 radius at 36 months was measured in a substudy of 309 patients. Results: At 36 months, significantly more patients in the denosumab arm had increases of >3% BMD from baseline at each site studied compared with placebo (LS, 78 vs 17%; FN, 48 vs 13%; TH, 48 vs 6%; distal 1/3 radius, 40 vs 7% (P

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Organisations: Prostate cancer research center (PCRC), Urology Associates Urologic Medical Research, Succ. Centre-Ville, Massachusetts General Hospital, Tampere University Hospital, Androgeos, Urological Associates of Lancaster, Amgen Incorporated
Contributors: Egerdie, R. B., Saad, F., Smith, M. R., Tammela, T. L. J., Heracek, J., Sieber, P., Ke, C., Leder, B., Dansey, R., Goessl, C.
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Original language: English
ASJC Scopus subject areas: Oncology, Urology, Cancer Research
Keywords: androgen deprivation, antiresorptive therapy, bone loss, bone mineral density, responder analysis
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Research output: Contribution to journal › Article › Scientific › peer-review

Obesity and physical inactivity are related to impaired physical health of breast cancer survivors

Aim: The aim of the present study was to examine the impact of obesity and physical activity on the health and wellbeing of patients with breast cancer shortly after the adjuvant treatments. Patients and Methods: A total of 537 women aged 35 to 68 years with newly-diagnosed breast cancer were enrolled into the exercise intervention study. The physical activity, physical performance (2-km walking test), cardiovascular risk factors, quality of life (EORTC-QoL-C30), co-morbidities and body-mass index (BMI) were measured after the adjuvant treatments. Results: Overall, 191 (39%) patients were overweight (BMI=25-30) and 85 (17%) obese (BMI≥30). Physical activity and performance (p

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Helsinki University Central Hospital, Tampere University Hospital, Pirkanmaa Cancer Societies, National Institutes for Health and Welfare, Helsinki Metropolia University of Applied Sciences, Turku University Hospital, Central Finland Central Hospital, Medcare Foundation
Contributors: Elme, A., Utriainen, M., Kellokumpu-Lehtinen, P., Palva, T., Luoto, R., Nikander, R., Huovinen, R., Kautiainen, H., Järvenpää, S., Penttinen, H. M., Vehmanen, L., Jääskeläinen, A. S., Ruohola, J., Blomqvist, C., Saarto, T.
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Source ID: 84876761214
Research output: Contribution to journal › Article › Scientific › peer-review

Computational cancer biology: education is a natural key to many locks

Background: Oncology is a field that profits tremendously from the genomic data generated by high-throughput technologies, including next-generation sequencing. However, in order to exploit, integrate, visualize and interpret such high-dimensional data efficiently, non-trivial computational and statistical analysis methods are required that need to be developed in a problem-directed manner. Discussion: For this reason, computational cancer biology aims to fill this gap. Unfortunately, computational cancer biology is not yet fully recognized as a coequal field in oncology, leading to a delay in its maturation and, as an immediate consequence, an under-exploration of high-throughput data for translational research. Summary: Here we argue that this imbalance, favoring 'wet lab-based activities', will be naturally rectified over time, if the next generation of scientists receives an academic education that provides a fair and competent introduction to computational biology and its manifold capabilities. Furthermore, we discuss a number of local educational provisions that can be implemented on university level to help in facilitating the process of harmonization.

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Contributors: Emmert-Streib, F., Zhang, S. D., Hamilton, P.
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Optimal management of metastatic castration-resistant prostate cancer: Highlights from a European Expert Consensus Panel

The exponential growth of novel therapies for the treatment of metastatic castration-resistant prostate cancer (mCRPC) over the last decade has created an acute need for education and guidance of clinicians regarding optimal strategies for patient management. A multidisciplinary panel of 21 European experts in mCRPC assembled for comprehensive discussion and consensus development, seeking to move the field forward and provide guidance and perspectives on optimal selection and sequencing of therapeutic agents and monitoring of response to treatment and disease progression. A total of 110 clinically-relevant questions were addressed and a modified Delphi method was utilised to obtain a consensus. The panel reached a consensus on several important issues, providing recommendations on appropriate phase III clinical trial end-points and optimal strategies for imaging and monitoring of bone metastases. Guidance regarding selection and sequencing of therapy in patients with newly diagnosed or progressive mCRPC is emphasised, including the use of novel bone-targeted agents, chemotherapy, androgen receptor pathway-targeted agents and immunotherapy. The impact of drug resistance and prostate-specific antigen flare on treatment decisions was also addressed. Ultimately, individualised therapy for patients with mCRPC is dependent on continued refinement of clinical decision-making based on patient and disease characteristics. This consensus statement offers clinicians expert guidance on the implementation of recent advances to improve patient outcome, focusing on the future of prostate cancer care.

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European Code against Cancer 4th Edition: Medical exposures, including hormone therapy, and cancer

The 4th edition of the European Code against Cancer recommends limiting – or avoiding when possible – the use of hormone replacement therapy (HRT) because of the increased risk of cancer, nevertheless acknowledging that prescription of HRT may be indicated under certain medical conditions. Current evidence shows that HRT, generally prescribed as menopausal hormone therapy, is associated with an increased risk of cancers of the breast, endometrium, and ovary, with the risk pattern depending on factors such as the type of therapy (oestrogen-only or combined oestrogen–progestogen), duration of treatment, and initiation according to the time of menopause. Carcinogenicity has also been established for anti-neoplastic agents used in cancer therapy, immunosuppressants, oestrogen–progestogen contraceptives, and tamoxifen. Medical use of ionising radiation, an established carcinogen, can provide major health benefits; however, prudent practices need to be in place, with procedures and techniques providing the needed diagnostic information or therapeutic gain with the lowest possible radiation exposure. For pharmaceutical drugs and medical radiation exposure with convincing evidence on their carcinogenicity, health benefits have to be balanced against the risks; potential increases in long-term cancer risk should be considered in the context of the often substantial and immediate health benefits from diagnosis and/or treatment. Thus, apart from HRT, no general recommendations on reducing cancer risk were given for carcinogenic drugs and medical radiation in the 4th edition of European Code against Cancer. It is crucial that the application of these measures relies on medical expertise and thorough benefit–risk evaluation. This also pertains to cancer-preventive drugs, and self-medication with aspirin or other potential chemopreventive drugs is strongly discouraged because of the possibility of serious, potentially lethal, adverse events.

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Contributors: Friis, S., Kesminiene, A., Espina, C., Auvinen, A., Straif, K., Schüz, J.
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Strong FGFR3 staining is a marker for FGFR3 fusions in diffuse gliomas

Background. Inhibitors of fibroblast growth factor receptors (FGFRs) have recently arisen as a promising treatment option for patients with FGFR alterations. Gene fusions involving FGFR3 and transforming acidic coiled-coil protein 3 (TACC3) have been detected in diffuse gliomas and other malignancies, and fusion-positive cases have responded well to FGFR inhibition. As high FGFR3 expression has been detected in fusion-positive tumors, we sought to determine the clinical significance of FGFR3 protein expression level as well as its potential for indicating FGFR3 fusions. Methods. We performed FGFR3 immunohistochemistry on tissue microarrays containing 676 grades II-IV astrocytomas and 116 grades II-III oligodendroglial tumor specimens. Fifty-one cases were further analyzed using targeted sequencing. Results. Moderate to strong FGFR3 staining was detected in gliomas of all grades, was more common in females, and was associated with poor survival in diffuse astrocytomas. Targeted sequencing identified FGFR3-TACC3 fusions and an FGFR3-CAMK2A fusion in 10 of 15 strongly stained cases, whereas no fusions were found in 36 negatively to moderately stained cases. Fusion-positive cases were predominantly female and negative for IDH and EGFR/PDGFRA/MET alterations. These and moderately stained cases show lower MIB-1 proliferation index than negatively to weakly stained cases. Furthermore, stronger FGFR3 expression was commonly observed in malignant tissue regions of lower cellularity in fusion-negative cases. Importantly, subregional negative FGFR3 staining was also observed in a few fusion-positive cases. Conclusions. Strong FGFR3 protein expression is indicative of FGFR3 fusions and may serve as a clinically applicable predictive marker for treatment regimens based on FGFR inhibitors.

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European Code against Cancer 4th Edition: Ultraviolet radiation and cancer

Ultraviolet radiation (UVR) is part of the electromagnetic spectrum emitted naturally from the sun or from artificial sources such as tanning devices. Acute skin reactions induced by UVR exposure are erythema (skin reddening), or sunburn, and the acquisition of a suntan triggered by UVR-induced DNA damage. UVR exposure is the main cause of skin cancer, including cutaneous malignant melanoma, basal-cell carcinoma, and squamous-cell carcinoma. Skin cancer is the most common cancer in fair-skinned populations, and its incidence has increased steeply over recent decades. According to estimates for 2012, about 100,000 new cases of cutaneous melanoma and about 22,000 deaths from it occurred in Europe. The main mechanisms by which UVR causes cancer are well understood. Exposure during childhood appears to

be particularly harmful. Exposure to UVR is a risk factor modifiable by individuals' behaviour. Excessive exposure from natural sources can be avoided by seeking shade when the sun is strongest, by wearing appropriate clothing, and by appropriately applying sunscreens if direct sunlight is unavoidable. Exposure from artificial sources can be completely avoided by not using sunbeds. Beneficial effects of sun or UVR exposure, such as for vitamin D production, can be fully achieved while still avoiding too much sun exposure and the use of sunbeds. Taking all the scientific evidence together, the recommendation of the 4th edition of the European Code Against Cancer for ultraviolet radiation is: "Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds."

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Research output: Contribution to journal › Article › Scientific › peer-review

The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study

CombAT (Combination of Avodart and Tamsulosin) was a randomised, double-blind study in men (n4844) aged 50 years with a clinical diagnosis of BPH. Patients were randomised to daily tamsulosin 0.4 mg, dutasteride 0.5 mg or both for 4 years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary endpoints included BPH clinical progression, symptoms and maximum urinary flow rate. A post hoc analysis of data from the European subgroup was conducted. A total of 2925 men were randomised to treatment in Europe as part of CombAT (tamsulosin, n=972; dutasteride, n=970; combination, n=983). Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery compared with either monotherapy at 4 years, and also significantly reduced the risk of BPH clinical progression. Combination therapy also provided significantly greater symptom improvement than either monotherapy at 4 years. Safety and tolerability of dutasteride plus tamsulosin was consistent with previous experience of this combination and with the monotherapies. These data provide further evidence to support the use of long-term combination therapy (dutasteride plus tamsulosin) in men with moderate-to-severe lower urinary tract symptoms because of BPH and prostatic enlargement. The results in the European subgroup are generally consistent with those in the overall study population.

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Research output: Contribution to journal › Article › Scientific › peer-review

Cost-effectiveness of prostate cancer screening: A simulation study based on ERSPC data

Background: The results of the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial showed a statistically significant 29% prostate cancer mortality reduction for the men screened in the intervention arm and a 23% negative impact on the life-years gained because of quality of life. However, alternative prostate-specific antigen (PSA) screening strategies for the population may exist, optimizing the effects on mortality reduction, quality of life, overdiagnosis, and costs. Methods: Based on data of the ERSPC trial, we predicted the numbers of prostate cancers diagnosed, prostate cancer deaths averted, life-years and quality-adjusted life-years (QALY) gained, and cost-effectiveness of 68 screening strategies starting at age 55 years, with a PSA threshold of 3, using microsimulation modeling. The screening strategies varied by age to stop screening and screening interval (one to 14 years or once in a lifetime screens), and therefore number of tests. Results: Screening at short intervals of three years or less was more cost-effective than using longer intervals. Screening at ages 55 to 59 years with two-year intervals had an incremental cost-effectiveness ratio of $73 000 per QALY gained and was considered optimal. With this strategy, lifetime prostate cancer mortality reduction was predicted as 13%, and 33% of the screen-detected cancers were overdiagnosed. When better quality of life for the post-treatment period could be achieved, an older age of 65 to 72 years for ending screening was obtained. Conclusion: Prostate cancer screening can be cost-effective when it is limited to two or three screens between ages 55 to 59 years. Screening above age 63 years is less cost-effective because of loss of QALYs because of overdiagnosis.

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No additional benefit of adding ifosfamide to docetaxel in castration-resistant metastatic prostate cancer

Background: In the treatment of many types of cancer, combination chemotherapy has been shown to be better than single-agent chemotherapy. The aim of our phase I-II clinical trial was to assess the efficacy and toxicity of docetaxel-ifosfamide combination chemotherapy in patients with castration-resistant metastatic prostate cancer (CRPC). Patients and Methods: A total of 31 patients were enrolled to receive first-line chemotherapy consisting of 40-60 mg/m2 docetaxel followed by 3.0 g/ m2 ifosfamide with mesna. All drugs were administered intravenously. The maximum duration of the chemotherapy was six cycles. The median age of the patients was 70 (range 58-82) years. Prostate specific antigen (PSA) responses were determined according to the PSA working group guidelines and all toxicities, time-to-progression and overall survival were determined according to the WHO criteria. Results: The objective PSA response rate was 32% in 11/31 patients. The mean PSA value at baseline was 300 (range 2.5-1577) μg/l. The overall median survival was 14.1 months; 15 patients were alive at a median follow-up time of 18 months. The observed side-effects were as expected, with grade 3-4 neutropenia developing in 38% of the cycles, whereas febrile neutropenia occurred in only 12% of the patients. The median number of administered cycles was 4.8. No acute hypersensitivity reactions were observed. Transient renal insufficiency developed in two patients, thus necessitating dose reductions. Conclusion: The combination of docetaxel and ifosfamide seems to be well-tolerated and has some activity in patients with CRPC. However, newer docetaxel-based combination chemotherapy regimens need to be further developed in other to provide more efficacious and well-tolerated treatment options for earlier phases of CRPC.

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Effects of single and fractionated irradiation on natural killer cell populations: Radiobiological characteristics of viability and cytotoxicity in vitro

Background: Natural killer (NK) cells are important in destroying tumor cells. However, they are damaged by radiation therapy. We studied the effects of single and fractionated irradiation on the viability and cytotoxicity of human non-selected NK cells and sub-groups with cluster of differentiation (CD) CD16+ and CD56+ in vitro. Only very few studies dealing with the standard radiobiological parameters for characterizing NK cells exist in the literature. Materials and Methods: NK cell populations were isolated from buffy coats using different methods and irradiated with single doses up to 80 Gy and fractionated doses of 10 or 30 Gy with different numbers of applications and at different intervals. The study end-points were viability using propidium iodide (PI), trypan blue and intracellular adenosine triphosphate (ATP) assays, and cytotoxicity using the 51Cr-release assay. The standard radiobiological parameters α and β of the linear-quadratic (L-Q) model and the mean inactivation dose D taken as the area under the curve (AUC) were calculated to characterize the radiosensitivity of different NK cell populations. Results: The AUC values of the 51Cr release data in the dose range of 0-40 Gy were as follows: for non-selected NK cells, 23.6- 20.9 Gy; for CD16+ and CD56+ cells, 14.5-13.2 Gy. The AUC values of ATP, trypan blue and propidium iodide methods equally well described the viability of irradiated NK cells. The α/β ratio for cytotoxicity and viability data in the L-Q model corresponded to the acutely responding tissues. Splitting a 30-Gy dose into two fractions applied at different intervals caused a significant rise in ATP levels and cytotoxicity. Dividing the total dose into four doses applied at fixed intervals also resulted in significant elevations of ATP content and cytotoxicity of NK cells at 10 Gy. Conclusion: According to the L-Q method, irradiated NK cells behaved similarly to acutely responding human tissues with respect to cytotoxicity and viability. The AUC proved very useful for comparing the effects of irradiation on NK cells.

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Aneuploidy facilitates oncogenic transformation via specific genetic alterations, including Twist2 upregulation
Aneuploidy, deviation from the normal chromosome number, and other chromosomal aberrations are commonly observed in cancer. Integrin-mediated adhesion and dynamic turnover of adhesion sites are required for successful cytokinesis of normal adherent cells and impaired cell division can lead to the generation of cells with abnormal chromosome contents. We find that repeated cytokinesis failure, due to impaired integrin traffic alone, is sufficient to induce chromosome aberrations resulting in the generation of aneuploid cells with malignant properties. Here, we have compared isogenic aneuploid and euploid cell lines with unravel aneuploidy-induced changes in cellular signaling. Euploid, non-transformed, and aneuploid, transformed, cell lines were investigated using genome-wide gene expression profiling, analysis of deregulated biological pathways and array-comparative genomic hybridization. We find that aneuploidy drives malignancy via inducing marked changes in gene and micro RNA expression profiles and thus imposing specific growth and survival promoting alterations in cellular signaling. Importantly, we identify Twist2 as a key regulator of survival, invasion and anchorage-independent growth in the aneuploid cells. In addition, alterations in lipid biosynthetic pathways and miR-10b upregulation are likely contributors to the malignant phenotype.

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Contributors: Högnäs, G., Hämälistö, S., Rilla, K., Laine, J. O., Vilkki, V., Murumägi, A., Edgren, H., Kallioniemi, O., Ivaska, J.
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Cytokinesis failure due to derailed integrin traffic induces aneuploidy and oncogenic transformation in vitro and in vivo

Aneuploidy is frequently detected in solid tumors but the mechanisms regulating the generation of aneuploidy and their relevance in cancer initiation remain under debate and are incompletely characterized. Spatial and temporal regulation of integrin traffic is critical for cell migration and cytokinesis. Impaired integrin endocytosis, because of the loss of Rab21 small GTPase or mutations in the integrin B-subunit cytoplasmic tail, induces failure of cytokinesis in vitro. Here, we describe that repeatedly failed cytokinesis, because of impaired traffic, is sufficient to trigger the generation of aneuploid cells, which display characteristics of oncogenic transformation in vitro and are tumorigenic in vivo. Furthermore, in an in vivo mouse xenograft model, non-transformed cells with impaired integrin traffic formed tumors with a long latency. More detailed investigation of these tumors revealed that the tumor cells were aneuploid. Therefore, abnormal integrin traffic was linked with generation of aneuploidy and cell transformation also in vivo. In human prostate and ovarian cancer samples, downregulation of Rab21 correlates with increased malignancy. Loss-of-function experiments demonstrate that long-term depletion of Rab21 is sufficient to induce chromosome number aberrations in normal human epithelial cells. These data are the first to demonstrate that impaired integrin traffic is sufficient to induce conversion of non-transformed cells to tumorigenic cells in vitro and in vivo.

General information

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Novel Loci for Metabolic Networks and Multi-Tissue Expression Studies Reveal Genes for Atherosclerosis

Association testing of multiple correlated phenotypes offers better power than univariate analysis of single traits. We analyzed 6,600 individuals from two population-based cohorts with both genome-wide SNP data and serum metabolomic profiles. From the observed correlation structure of 130 metabolites measured by nuclear magnetic resonance, we identified 11 metabolic networks and performed a multivariate genome-wide association analysis. We identified 34 genomic loci at genome-wide significance, of which 7 are novel. In comparison to univariate tests, multivariate association analysis identified nearly twice as many significant associations in total. Multi-tissue gene expression studies identified variants in our top loci, SERPINA1 and AQP9, as eQTLs and showed that SERPINA1 and AQP9 expression in human blood was associated with metabolites from their corresponding metabolic networks. Finally, liver expression of AQP9 was associated with atherosclerotic lesion area in mice, and in human arterial tissue both SERPINA1 and AQP9 were shown to be upregulated (6.3-fold and 4.6-fold, respectively) in atherosclerotic plaques. Our study illustrates the power of multi-phenotype GWAS and highlights candidate genes for atherosclerosis.

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Contributors: Inouye, M., Ripatti, S., Kettunen, J., Lyytikäinen, L. P., Oksala, N., Laurila, P. P., Kangas, A. J., Soininen, P., Savolainen, M. J., Viikari, J., Kähönen, M., Perola, M., Salomaa, V., Raitakari, O., Lehtimäki, T., Taskinen, M. R., Järvelin, M. R., Ala-Korpela, M., Palotie, A., de Bakker, P. I. W.
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ASJC Scopus subject areas: Genetics, Molecular Biology, Ecology, Evolution, Behavior and Systematics, Cancer Research, Genetics(clinical)
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Research output: Contribution to journal › Article › Scientific › peer-review

Smoking cessation intervention in Rural Kerala, India: Findings of a randomised controlled trial
Background: Prevalence of tobacco use is higher in the rural than urban areas of India. Unlike tobacco cessation clinics located in urban areas, community-based smoking cessation intervention has the potential to reach a wider section of the community to assist in smoking cessation in the rural setting. The present study aimed to assess the effectiveness of a cessation intervention in rural Kerala state, India. Materials and Methods: Current daily smoking resident males in the age group 18-60 years from four community development blocks in rural Kerala were randomly allocated to intervention and control groups. The intervention group received multiple approaches in which priority was given to face-to-face interviews and telephone counselling. Initially educational materials on tobacco hazards were distributed. Further, four rounds of counselling sessions were conducted which included a group counselling with a medical camp as well as individual counselling by trained medical social workers. The control group received general awareness training on tobacco hazards along with an anti-tobacco leaflet. Self-reported smoking status was assessed after 6 and 12 months. Factors associated with tobacco cessation were estimated using binomial regression method. Results: Overall prevalence of smoking abstinence was 14.7% in the intervention and 6.8% in the control group (Relative risk: 1.85, 95% CI: 1.05, 3.25). A total of 41.3% subjects in the intervention area and 13.6% in the control area had reduced smoking by 50% or more at the end of 12 months. Lower number of cigarettes/bidi used, low nicotine dependence and consultation with a doctor for a medical ailment were the statistically significant predictors for smoking cessation. Conclusions: Rigorous approaches for smoking cessation programmes can enhance quit rates in smoking in rural areas of India.

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Organisations: Prostate cancer research center (PCRC), Regional Cancer Centre India, National Public Health Institute
Contributors: Jayakrishnan, R., Uutela, A., Mathew, A., Auvinen, A., Mathew, P. S., Sebastian, P.
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Source ID: 84892473555
Research output: Contribution to journal › Article › Scientific › peer-review

Multiple approaches and participation rate for a community based smoking cessation intervention trial in rural Kerala, India

Background: To illustrate multiple approaches and to assess participation rates adopted for a community based smoking cessation intervention programme in rural Kerala. Materials and Methods: Resident males in the age group 18-60 years who were 'current daily smokers' from 4 randomly allocated community development blocks of rural Thiruvananthapuram district, Kerala (2 intervention and 2 control groups) were selected. Smoking status was assessed through house-to-house survey using trained volunteers. Multiple approaches included awareness on tobacco hazards during baseline survey and distribution of multicolour anti-tobacco leaflets for intervention and control groups. Further, the intervention group received a tobacco cessation booklet and four sessions of counselling which included a one-time group counselling cum medical camp, followed by proactive counselling through face-to-face (FTF) interview and mobile phone. In the second and fourth session, motivational counselling was conducted. Results: Among 928 smokers identified, smokers in intervention and control groups numbered 474 (mean age: 44.6 years, SD: 9.66 years) and 454 respectively (44.5 years, SD: 10.30 years). Among the 474 subjects, 75 (16%) had attended the group counselling cum medical camp after completion of baseline survey in the intervention group, Among the remaining subjects (n=399), 88% were contacted through FTF and mobile phone (8.5%). In the second session (4-6 weeks time period), the response rate for individual counselling was 94% (78% through FTF and 16% through mobile phone). At 3 months, 70.4% were contacted by their mobile phone and further, 19.6% through FTF (total 90%) while at 6 months (fourth session), the response rate was 74% and 16.4% for FTF and mobile phone respectively, covering 90.4% of the total subjects. Overall, in the intervention group, 97.4% of subjects were being contacted at least once and individual counselling given. Conclusion: Proactive community centred intervention programmes using multiple approaches were found to be successful to increase the participation rate for intervention.

General information

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Contributors: Jayakrishnan, R., Mathew, A., Uutela, A., Auvinen, A., Sebastian, P.
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Source ID: 84880347929
Research output: Contribution to journal › Article › Scientific › peer-review

Adjuvant capecitabine, docetaxel, cyclophosphamide,and epirubicin for early breast cancer: Final analysis of the randomized FinXX trial

Purpose: Capecitabine is an active agent in the treatment of breast cancer. It is not known whether integration of capecitabine into an adjuvant regimen that contains a taxane, an anthracycline, and cyclophosphamide improves outcome in early breast cancer. Patients and Methods: Women with axillary node-positive or high-risk node-negative breast cancer were randomly assigned to receive either three cycles of docetaxel and capecitabine (TX) followed by three cycles of cyclophosphamide, epirubicin, and capecitabine (CEX; n = 753) or three cycles of docetaxel (T) followed by three cycles of cyclophosphamide, epirubicin, and fluorouracil (CEF; n = 747). The primary end point was recurrence-free survival (RFS). Results: During a median follow-up time of 59 months, 214 RFS events occurred (local or distant recurrences or deaths; TX/CEX, n = 96; T/CEF, n = 118). RFS was not significantly different between the groups (hazard ratio [HR], 0.79; 95% CI, 0.60 to 1.04; P = .087; 5-year RFS, 86.6% for TX/CEX v 84.1% for T/CEF). Fifty-six patients assigned to TX/CEX died during the follow-up compared with 75 of patients assigned to T/CEF (HR, 0.73; 95% CI, 0.52 to 1.04; P = .080). In exploratory analyses, TX/CEX improved breast cancer-specific survival (HR, 0.64; 95% CI, 0.44 to 0.95; P = .027) and RFS in women with triple-negative disease and in women who had more than three metastatic axillary lymph nodes at the time of diagnosis. We detected little severe late toxicity. Conclusion: Integration of capecitabine into a regimen that contains docetaxel, epirubicin, and cyclophosphamide did not improve RFS significantly compared with a similar regimen without capecitabine.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Helsinki University Central Hospital, Tampere University Hospital, Turku University Hospital, Oulu University Hospital, Kanta-Häme Central Hospital, Gävle Hospital, University Central Hospital Kuopio, Kotka Central Hospital, Örebro University Hospital, Päijät-Häme Central Hospital, Uppsala University Hospital, Jyvaskyla Central Hospital, Satakunta Central Hospital, 4Pharma, Vaasa Central Hospital
Contributors: Joensuu, H., Kellokumpu-Lehtinen, P. L., Huovinen, R., Jukkola-Vuorinen, A., Tanner, M., Kokko, R., Ahlgren, J., Auvinen, P., Paija, O., Helle, L., Villman, K., Nyandoto, P., Nilsson, G., Pajunen, M., Asola, R., Poikonen, P., Leinonen, M., Kataja, V., Bono, P., Lindman, H.
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Research output: Contribution to journal › Article › Scientific › peer-review

Sotalol, but not digoxin is associated with decreased prostate cancer risk: A population-based case-control study

Antiarrhythmic drug digoxin has been reported to have apoptosis-inducing and cytotoxic effects on prostate cancer cells. We evaluated the association between antiarrhythmic drug use and prostate cancer risk in a population-based case-control study. The study included all new prostate cancer cases diagnosed in Finland during 1995-2002 and matched controls (24,657 case-control pairs) obtained from the Finnish Cancer Registry and the Population Register Center, respectively. Information on antiarrhythmic drug purchases was obtained from national prescription database. Multivariable-adjusted conditional logistic regression model was used for data analysis. Compared to never-users of antiarrhythmic drugs, we found no significant association between digoxin use and prostate cancer risk overall [odds ratio (OR) 0.95, 95% confidence interval (CI): 0.89-1.01] or for advanced prostate cancer risk (OR: 0.90, 95% CI: 0.77-1.05). The result was similar also for other antiarrhythmic drugs, with the exception of sotalol, users of which had decreased risk of advanced prostate cancer (OR: 0.73, 95% CI: 0.56-0.96). Also the overall prostate cancer risk decreased by duration of sotalol use (p for trend 0.038). We show that digoxin or other common antiarrhythmic drugs generally do not associate with prostate cancer risk at population level during maximum follow-up of eight years. However, we cannot rule out longer

term protective effects of digoxin. K^+-channel blocker sotalol shows some promise as prostate cancer preventing agent. However, findings need to be confirmed in further studies. What's new? The antiarrhythmic drug digoxin triggers apoptosis in prostate cancer cells, and recent research suggests that the drug may even reduce prostate cancer risk. In the present population-based case-control study, which included data on more than 25,000 Finnish men, digoxin and other antiarrhythmic drugs, with the exception of sotalol, were found to have no impact on prostate cancer risk. By contrast, sotalol, which possesses both beta-blocker and K+-channel inhibitor activity, was inversely associated with overall risk and risk of advanced prostate cancer. If validated, sotalol may prove to be of greater relevance to prostate cancer prevention than digoxin.

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Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Johns Hopkins Bloomberg School of Public Health
Contributors: Kaapu, K. J., Ahti, J., Tammela, T. L. J., Auvinen, A., Murtola, T. J.
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Research output: Contribution to journal › Article › Scientific › peer-review

Effects of remedies made in patient setup process on residual setup errors and margins in head and neck cancer radiotherapy based on 2D image guidance
Aim: Patient setup errors were aimed to be reduced in radiotherapy (RT) of head-and-neck (H&N) cancer. Some remedies in patient setup procedure were proposed for this purpose. Background: RT of H&N cancer has challenges due to patient rotation and flexible anatomy. Residual position errors occurring in treatment situation and required setup margins were estimated for relevant bony landmarks after the remedies made in setup process and compared with previous results. Materials and methods: The formation process for thermoplastic masks was improved. Also image matching was harmonized to the vertebrae in the middle of the target and a 5 mm threshold was introduced for immediate correction of systematic errors of the landmarks. After the remedies, residual position errors of bony landmarks were retrospectively determined from 748 orthogonal X-ray images of 40 H&N cancer patients. The landmarks were the vertebrae C1-2, C5-7, the occiput bone and the mandible. The errors include contributions from patient rotation, flexible anatomy and inter-observer variation in image matching. Setup margins (3D) were calculated with the Van Herk formula. Results: Systematic residual errors of the landmarks were reduced maximally by 49.8% ($p \leq 0.05$) and the margins by 3.1 mm after the remedies. With daily image guidance the setup margins of the landmarks were within 4.4 mm, but larger margins of 6.4 mm were required for the mandible. Conclusions: Remarkable decrease in the residual errors of the bony landmarks and setup margins were achieved through the remedies made in the setup process. The importance of quality assurance of the setup process was demonstrated.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, Department of Medical Physics
Contributors: Kapanen, M., Laaksomaa, M., Tulijoki, T., Kellokumpu-Lehtinen, P. L., Hyödynmaa, S.
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Keywords: Head and neck cancer, Image guidance, Patient setup, Radiotherapy, Setup margins
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Source ID: 84931578426
Research output: Contribution to journal › Article › Scientific › peer-review

Bi-weekly paclitaxel and capecitabine as a second- Or third-line treatment for advanced breast cancer: A pilot study
Background: Chemotherapy given every third week is currently the mainstay in the treatment of metastatic breast cancer (MBC). However, bi-weekly dosing might offer a better dose intensity, with better tolerability and response rates. This hypothesis was tested in a phase II study on bi-weekly paclitaxel combined with capecitabine. Patients and Methods: Nineteen patients [median age was 60 (range: 43-68) years] with MBC were treated with paclitaxel (Taxol ®) 120 mg/m^2 ,with 1-h infusion on days 1 and 15, and capecitabine (Xeloda ®) 2650 mg/m^2/day orally given at two doses on days 1-7 and 15-21 on a 28-day cycle. Metastatic sites included the bone (68%), lung (63%) and liver (47%), and 95% of patients had more than one sites of metastasis. Results: In the response evaluation, one complete and 12 partial responses (overall response rate 68%), two stable disease cases and two progressive disease cases were observed. The median duration of response was 13.4 (range: 3.9-43.5) months. Progression-free and overall survival were 13 (95% CI=10.8-15.3) months and 23 (95% CI=17.7-29.1), respectively. A total of 140 (median 8, range 1-28) cycles were delivered. Grade 3-4 toxicity was uncommon: neutropenia was observed in 5% of the cycles; pulmonary problems in 1.4%; pain in 1.4%; and hand-and-foot syndrome, tiredness and arthralgia/myalgia, each in 0.7% of the study treatment cycles. Conclusion: Bi-weekly dosing of paclitaxel and capecitabine seems to yield promising responses in advanced breast cancer, with an acceptable adverse-event profile.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital
Contributors: Kellokumpu-Lehtinen, P. L., Tuunanen, T., Kautio, A. L., Lehtinen, I., Tanner, M.
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Source: Scopus
Source ID: 84891364452
Research output: Contribution to journal › Article › Scientific › peer-review

Weekly paclitaxel-An effective treatment for advanced breast cancer
Aim: Weekly paclitaxel is widely used in the treatment of metastatic breast cancer (MBC). Our aim was to test its efficacy and tolerability as a second-line therapy for MBC in daily oncology practice. Patients and Methods: Paclitaxel (90 mg/m2)

was given intravenously three times weekly in a 4-week cycle to 91 patients with disease progression after hormonal (42%) or cytostatic therapy (57%). The median age was 54 years; metastatic sites were the lung (39%), liver (52%) and bone (47%). 64% of patients had more than one site of metastasis. Results: Median time- to-progression was 7.5 months (range=6.5-8.5 months) and median overall survival time was 20.1 months (range=13.7-26.5 months). We observed 10 complete (12%) and 37 partial (43%) responses (an overall response rate of 55%). Severe side-effects were rare (grade 3-4 neutropenia 13% and septic episodes in three cases). Conclusion: Weekly paclitaxel was shown to be an effective and well-tolerated treatment for advanced breast cancer.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Tampere, Medical School, Satakunta Central Hospital, Turku University Hospital, Oulu University Hospital, Department of Oncology Hämeenlinna Central Hospital, Rovaniemi Central Hospital, Kemi Central Hospital, Kajaani Central Hospital, Lappeenranta Central Hospital, Seinäjoki Central Hospital
Contributors: Kellokumpu-Lehtinen, P., Tuunanen, T., Asola, R., Elomaa, L., Heikkinen, M., Kokko, R., Järvenpää, R., Lehtinen, I., Maiche, A., Kaleva-Kerola, J., Huusko, M., Möykkynen, K., Ala-Luhtala, T.
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Toxicity in patients receiving adjuvant docetaxel hormonal treatment after radical radiotherapy for intermediate or high-risk prostate cancer: A preplanned safety report of the SPCG-13 trial

Background: Radical radiotherapy (RT) combined with androgen deprivation therapy is currently the standard treatment for elderly patients with localized intermediate- or high-risk prostate cancer (PC). To increase the recurrence-free and overall survival, we conducted an adjuvant, randomized trial using docetaxel (T) in PC patients (Scandinavian Prostate Cancer Group trial 13). Methods: The inclusion criteria are the following: Men >18 and ≤75 years of age, WHO/ECOG performance status 0-1, histologically proven PC within 12 months before randomization and one of the following: T2, Gleason 7 (4+3), PSA > 10; T2, Gleason 8-10, any PSA; or any T3 tumors. Neoadjuvant/adjuvant hormone therapy is mandatory for all patients. The patients were randomized to receive six cycles of T (75 mg m^{-2} d 1. cycle 21 d) or no docetaxel after radical RT (with a minimum tumor dose of 74 Gy). This study identifier number is NTC 006653848 (http://www.clinicaltrials.org). Results: In this preplanned safety analysis of 100 patients, T treatment induced grade (G) 3 adverse events (AEs) in 15 patients (30%) and G4 AEs in 30 patients (60%), mainly due to bone marrow toxicity. Neutropenia G3-4 was observed in 72% of the patients, febrile neutropenia was found in 24% of patients, neutropenic infection in 10% of patients and G3 infection without neutropenia in 4% of patients. Nonhematological G3 AEs were rare: Anorexia, diarrhea, mucositis, nausea, pain (1 patient each) and fatigue (5). Other severe serious AEs related to T were pulmonary embolism and renal failure. However, only three patients discontinued T before completing the planned six cycles. No deaths had occurred. No patients in the control arm experienced G3-4 toxicities at 12 weeks after the randomization. Conclusions: Adjuvant docetaxel chemotherapy after radiotherapy has a higher frequency of neutropenia than previous studies on patients with metastatic disease. Otherwise, the treatment was quite well tolerated.

General information

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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, Karolinska University Hospital, Umeå University Hospital, Uppsala University Hospital, Sundsvall University Hospital, Seinäjoki Central Hospital, Växjö Central Hospital, 4Pharma, Karlstad Central Hospital
Contributors: Kellokumpu-Lehtinen, P. L., Hjälm-Eriksson, M., Thellenberg-Karlsson, C., Åström, L., Franzen, L., Marttila, T., Seke, M., Taalikka, M., Ginman, C.

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Issue number: 3
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ASJC Scopus subject areas: Oncology, Urology, Cancer Research
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DOIs:

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Research output: Contribution to journal › Article › Scientific › peer-review

The association between antihypertensive drug use and incidence of prostate cancer in Finland: A population-based case-control study
Some studies have suggested that use of antihypertensive drugs could decrease prostate cancer risk. We evaluated this association at the population level. All prostate cancer cases in Finland during 1995-2002 and matched controls (24,657 case-control pairs) were identified from the Finnish Cancer Registry and the Population Register Center, respectively. Detailed information on antihypertensive drug purchases was obtained from a national prescription database. Data were analyzed using multivariable-adjusted conditional logistic regression model. Ever use of antihypertensive drugs was associated with marginally elevated overall prostate cancer risk (OR 1.16; 95% CI, 1.12-1.21). Risk of advanced prostate cancer did not differ from the nonusers (OR 1.08, 95% CI 0.98-1.18). The risk increase was observed constantly in all classes of antihypertensive drugs. Our large populationbased study generally does not support decreased risk of prostate cancer among antihypertensive drug users. Conversely, an increased overall prostate cancer risk was observed. The association being similar for all drug groups suggests that it is probably caused by a systematic difference between medication users and nonusers, such as differing PSA testing activity.

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Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Central Finland Hospital
Contributors: Kemppainen, K. J., Tammela, T. L. J., Auvinen, A., Murtola, T. J.
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Volume: 22
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Original language: English
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Chk1 targeting reactivates PP2A tumor suppressor activity in cancer cells

Checkpoint kinase Chk1 is constitutively active in many cancer cell types and new generation Chk1 inhibitors show marked antitumor activity as single agents. Here we present a hitherto unrecognized mechanism that contributes to the response of cancer cells to Chk1-targeted therapy. Inhibiting chronic Chk1 activity in cancer cells induced the tumor suppressor activity of protein phosphatase protein phosphatase 2A (PP2A), which by dephosphorylating MYC serine 62, inhibited MYC activity and impaired cancer cell survival. Mechanistic investigations revealed that Chk1 inhibition activated PP2A by decreasing the transcription of cancerous inhibitor of PP2A (CIP2A), a chief inhibitor of PP2A activity. Inhibition of cancer cell clonogenicity by Chk1 inhibition could be rescued in vitro either by exogenous expression of CIP2A or by blocking the CIP2A-regulated PP2A complex. Chk1-mediated CIP2A regulation was extended in tumor models dependent on either Chk1 or CIP2A. The clinical relevance of CIP2A as a Chk1 effector protein was validated in several human cancer types, including neuroblastoma, where CIP2A was identified as an NMYC-independent prognostic factor. Because the Chk1-CIP2A-PP2A pathway is driven by DNA-PK activity, functioning regardless of p53 or ATM/ATR status, our results offer explanative power for understanding how Chk1 inhibitors mediate single-agent anticancer efficacy. Furthermore, they define CIP2A-PP2A status in cancer cells as a pharmacodynamicmarker for their response to Chk1-targeted therapy.

General information

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Organisations: Prostate cancer research center (PCRC), University of New South Wales (UNSW) Australia, Turku Doctoral Program of Biomedical Sciences (TuBS), FIN-00014 University of Helsinki, Karlsruhe Institute of Technology, Insitute for Technical Physics, Germany, University of Helsinki, Akdeniz University, School of Management (JKK), Turku Centre for Biotechnology, Children's Hospital of Philadelphia, Haartman Institute, University of Pennsylvania School of Medicine, Turun Yliopisto/Turun Biomateriaalikeskus
Contributors: Khanna, A., Kauko, O., Böckelman, C., Laine, A., Schreck, I., Partanen, J. I., Szwajda, A., Bormann, S., Bilgen, T., Helenius, M., Pokharel, Y. R., Pimanda, J., Russel, M. R., Haglund, C., Cole, K. A., Klefström, J., Aittokallio, T., Weiss, C., Ristimäki, A., Visakorpi, T., Westermarck, J.
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The Finnish prostate cancer screening trial: Analyses on the screening failures

Prostate cancer (PC) screening with prostate-specific antigen (PSA) has been shown to decrease PC mortality in the European Randomized Study of Screening for Prostate Cancer (ERSPC). However, in the Finnish trial, which is the largest component of the ERSPC, no statistically significant mortality reduction was observed. We investigated which had the largest impact on PC deaths in the screening arm: non-participation, interval cancers or PSA threshold. The screening (SA) and control (CA) arms comprised altogether 80,144 men. Men in the SA were screened at four-year intervals and referred to biopsy if the PSA concentration was ≥4.0 ng/ml, or 3.0-3.99 ng/ml with a free/total PSA ratio ≤16%. The median follow-up was 15.0 years. A counterfactual exclusion method was applied to estimate the effect of three subgroups in the SA: the non-participants, the screen-negative men with PSA ≥3.0 ng/ml and a subsequent PC diagnosis, and the men with interval PCs. The absolute risk of PC death was 0.76% in the SA and 0.85% in the CA; the observed hazard ratio (HR) was 0.89 (95% confidence interval (CI) 0.76-1.04). After correcting for non-attendance, the HR was 0.78 (0.64-0.96); predicted effect for a hypothetical PSA threshold of 3.0 ng/ml the HR was 0.88 (0.74-1.04) and after eliminating the effect of interval cancers the HR was 0.88 (0.74-1.04). Non-participating men in the SA had a high risk of PC death and a large impact on PC mortality. A hypothetical lower PSA threshold and elimination of interval cancers would have had a less pronounced effect on the screening impact.

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Contributors: Kilpeläinen, T. P., Tammela, T. L. J., Malila, N., Hakama, M., Santti, H., Määttänen, L., Stenman, U. H., Kujala, P., Auvinen, A.
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Prostate cancer mortality in the finnish randomized screening trial
BackgroundProstate cancer (PC) screening with prostate-specific antigen (PSA) has been shown to decrease PC mortality by the European Randomized Study of Screening for Prostate Cancer (ERSPC). We evaluated mortality results in the Finnish Prostate Cancer Screening Trial, the largest component of ERSPC. The primary endpoint was PC-specific mortality.MethodsA total of 80 144 men were identified from the population registry and randomized to either a screening arm (SA) or a control arm (CA). Men in the SA were invited to serum PSA determination up to three times with a 4-year interval between each scan and referred to biopsy if the PSA concentration was greater than or equal to 4.0ng/mL or 3.0 to 3.99ng/mL with a free/total PSA ratio less than or equal to 16%. Men in the CA received usual care. The analysis covers follow-up to 12 years from randomization for all men. Hazard ratios (HRs) were estimated for incidence and mortality using Cox proportional hazard model. All statistical tests were two-sided.ResultsPC incidence was 8.8 per 1000 person-years in the SA and 6.6 in the CA (HR = 1.34, 95% confidence interval [CI] = 1.27 to 1.40). The incidence of advanced PC was lower in the SA vs CA arm (1.2 vs 1.6, respectively; HR = 0.73, 95% CI = 0.64 to 0.82; P

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False-positive screening results in the European randomized study of screening for prostate cancer

Background: Screening for prostate cancer (PC) with prostate-specific antigen (PSA) has been shown to decrease mortality, but has adverse effects, such as false-positive (FP) screening results. We describe the frequency of FP results and assess their relation to subsequent screening attendance, test results and prostate cancer risk in a large randomized trial. Materials and methods: We included data from five centres of the European Randomized Study of Screening for Prostate Cancer, altogether over 61,000 screened men. Men were screened with PSA test at a 2-7 year interval depending on the centre; PSA cut-off was 3.0-4.0 ng/ml. A positive screen with no histologically confirmed PC in biopsy within 1 year was defined as an FP result. Results: Of the 61,604 men who were screened at least once, 17.8% had one or more FP result(s). Almost 20% of men who participated at all screening rounds had one or more FP result(s). More than half of the men with an FP result had another FP if screened again. Men with FP results had a fourfold risk of PC at subsequent screen (depending on the round, 10.0% versus 2.6-2.7% of men with negative screen, risk ratio 3.8-3.9). The PCs following an FP result were in 92.8% of cases localised and low-grade versus 90.4% following a screen-negative result. Conclusions: Our results show that FP results are common adverse effects in PC screening, as they affect at least one in six screened men. False-positive men are more prone to be diagnosed with PC but are also likely to have consistently high PSA levels.

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AR and ERG drive the expression of prostate cancer specific long noncoding RNAs

Long noncoding RNAs (lncRNAs) play pivotal roles in cancer development and progression, and some function in a highly cancer-specific manner. However, whether the cause of their expression is an outcome of a specific regulatory mechanism or nonspecific transcription induced by genome reorganization in cancer remains largely unknown. Here, we investigated a group of lncRNAs that we previously identified to be aberrantly expressed in prostate cancer (PC), called TPCATs. Our high-throughput real-time PCR experiments were integrated with publicly available RNA-seq and ChIP-seq data and revealed that the expression of a subset of TPCATs is driven by PC-specific transcription factors (TFs), especially androgen receptor (AR) and ETS-related gene (ERG). Our in vitro validations confirmed that AR and ERG regulated a subset of TPCATs, most notably for EPCART. Knockout of EPCART was found to reduce migration and proliferation of the PC cells in vitro. The high expression of EPCART and two other TPCATs (TPCAT-3-174133 and TPCAT-18-31849) were also associated with the biochemical recurrence of PC in prostatectomy patients and were

independent prognostic markers. Our findings suggest that the expression of numerous PC-associated lncRNAs is driven by PC-specific mechanisms and not by random cellular events that occur during cancer development. Furthermore, we report three prospective prognostic markers for the early detection of advanced PC and show EPCART to be a functionally relevant lncRNA in PC.

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Intraepidermal nerve fibre density in cancer patients receiving adjuvant chemotherapy
Background: Chemotherapy-induced neuropathy is a common adverse event in patients receiving vinca alcaloids, platinum derivatives and taxanes. However, the underlying pathogenetic mechanisms have not been completely elucidated. We set up a prospective pilot study on skin biopsies in newly diagnosed cancer patients receiving neurotoxic chemotherapeutic agents as adjuvant treatment in order to study the occurrence of small-fibre pathology and its relationship to clinical symptoms. Patients and Methods: Skin biopsies from distal leg were performed in 12 patients before, during and after chemotherapy. Using light microscopy, the intraepidermal nerve fibre (IENF) density was determined from the skin biopsies by counting morphometrically the immunopositive nerves per epidermal area. Results: Reduced IENF density was observed in eight patients at baseline. During the follow-up, the IENF density increased significantly in six patients and remained unchanged in two. In four patients, the IENF density was normal both at baseline and at the end of the follow-up period. Neuropathic symptoms were manifested in nine patients, but no association with the IENF count was found. Conclusion: During chemotherapy, results from patients revealed different evolutionary patterns of IENF density, but symptoms and IENF density were not related.

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Contributors: Koskinen, M. J., Kautio, A. L., Haanpää, M. L., Haapasalo, H. K., Kellokumpu-Lehtinen, P. L., Saarto, T., Hietaharju, A. J.
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Hypermethylation of the GABRÊmiR-452miR-224 promoter in prostate cancer predicts biochemical recurrence after radical prostatectomy

Purpose: Available tools for prostate cancer diagnosis and prognosis are suboptimal and novel biomarkers are urgently needed. Here, we investigated the regulation and biomarker potential of the GABRÊmiR-452miR-224 genomic locus. Experimental Design: GABRE/miR-452/miR-224 transcriptional expression was quantified in 80 nonmalignant and 281 prostate cancer tissue samples. GABRÊmiR-452miR-224 promoter methylation was determined by methylation-specific qPCR (MethyLight) in 35 nonmalignant, 293 prostate cancer [radical prostatectomy (RP) cohort 1] and 198 prostate cancer tissue samples (RP cohort 2). Diagnostic/prognostic biomarker potential of GABRÊmiR- 452miR-224 methylation was evaluated by ROC, Kaplan-Meier, uni- and multivariate Cox regression analyses. Functional roles of miR-224 and miR-452 were investigated in PC3 and DU145 cells by viability, migration, and invasion assays and gene-set enrichment analysis (GSEA) of posttransfection transcriptional profiling data. Results: GABRÊmiR-452miR-224 was significantly downregulated in prostate cancer compared with nonmalignant prostate tissue and had highly cancer-specific aberrant promoter hypermethylation (AUC = 0.98). Functional studies and GSEA suggested that miR-224 and miR-452 inhibit proliferation, migration, and invasion of PC3 and DU145 cells by direct/indirect regulation of pathways related to the cell cycle and cellular adhesion and motility. Finally, in uni- and multivariate analyses, high GABRÊmiR-452miR-224 promoter methylation was significantly associated with biochemical recurrence in RP cohort 1, which was successfully validated in RP cohort 2. Conclusion: The GABRÊmiR-452miR-224 locus is downregulated and hypermethylated in prostate cancer and is a new promising epigenetic candidate biomarker for prostate cancer diagnosis and prognosis. Tumor-suppressive functions of the intronic miR-224 and miR-452 were demonstrated in two prostate cancer cell lines, suggesting that epigenetic silencing of GABRÊmiR-452miR-224 may be selected for in prostate cancer.

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Contributors: Kristensen, H., Haldrup, C., Strand, S., Mundbjerg, K., Mortensen, M. M., Thorsen, K., Ostenfeld, M. S., Wild, P. J., Arsov, C., Goering, W., Visakorpi, T., Egevad, L., Lindberg, J., Grönberg, H., Høyer, S., Borre, M., Orntoft, T. F., Sørensen, K. D.
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Paclitaxel, carboplatin and 1,25-D3 inhibit proliferation of ovarian cancer cells in vitro

Background/Aim: The combination of paclitaxel and carboplatin is the standard chemotherapy for ovarian cancer. Previous studies have implied that vitamin D (1,25-D3) may have growth inhibitory effects in ovarian cancer. This study aimed to investigate the effect of paclitaxel, carboplatin and 1,25-D3 on the growth of ovarian cancer cells in vitro, based on the

hypothesis that 1,25-D3 might potentiate the effect of paclitaxel and/or carboplatin. Materials and Methods: Three non-commercial ovarian carcinoma cell lines UT-OV-1(mucinous), UT-OV-3B (serous) and UT-OV-4 (endometrioid) were exposed to different concentrations of 1,25-D3, paclitaxel and carboplatin, respectively. The cell viability was measured using a Crystal violet assay kit. The cellular vitamin D receptor (VDR) mRNA levels were measured by qRT-PCR using the LightCycler equipment. Results: The growth-inhibitory effect of the combination of paclitaxel and carboplatin was 56% in UT-OV-1, 33% in UT-OV-3B and 47% in UT-OV-4 cells. Single 1,25-D3 (10 μM) inhibited the growth of UT-OV-3B and UT-OV-4 by 23% and 28%, respectively, whereas no effect was seen in UT-OV-1 cells. These results are in line with the finding that the expression of VDR was high in UT-OV-3B and UT-OV-4, but very low in UT-OV-1. The combination of 1,25-D3, paclitaxel and carboplatin resulted in 61%, 46% and 58% growth reduction in UT-OV-1, UT-OV-3B and UT-OV-4 cells, respectively. The additive effect of 1,25-D3 was 21% in UT-OV-4, 20% in UT-OV-3B and 12% in UT-OV-1 cell line. Conclusion: The results imply that combining 1,25-D3 with paclitaxel and carboplatin may potentiate their growth inhibitory effect on ovarian cancer cells with high VDR expression.

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Contributors: Kuittinen, T., Rovio, P., Luukkaala, T., Laurila, M., Grénman, S., Kallioniemi, A., Mäenpää, J.
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Fallout from the Chernobyl accident and overall cancer incidence in Finland
Aim: We studied whether incidence of all cancer sites combined was associated with the radiation exposure due to fallout from the Chernobyl accident in Finland. An emphasis was on the first decade after the accident to assess the suggested "promotion effect". Methods: The segment of Finnish population with a stable residence in the first post-Chernobyl year (2. million people) was studied. The analyses were based on a 250 m × 250. m grid squares covering all of Finland and all cancer cases except cancers of the breast, prostate and lung. Cancer incidence in four exposure areas (based on first-year dose due to external exposure

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Contributors: Kurttio, P., Seppä, K., Pasanen, K., Patama, T., Auvinen, A., Pukkala, E., Heinävaara, S., Arvela, H., Hakulinen, T.
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The Effects of Pharmacological Compounds on Beat Rate Variations in Human Long QT-Syndrome Cardiomyocytes

Healthy human heart rate fluctuates overtime showing long-range fractal correlations. In contrast, various cardiac diseases and normal aging show the breakdown of fractal complexity. Recently, it was shown that human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) intrinsically exhibit fractal behavior as in humans. Here, we investigated the fractal complexity of hiPSC-derived long QT-cardiomyocytes (LQT-CMs). We recorded extracellular field potentials from hiPSC-CMs at baseline and under the effect of various compounds including β-blocker bisoprolol, ML277, a specific and potent I_{Ks} current activator, as well as JNJ303, a specific I_{Ks} blocker. From the peak-to-peak-intervals, we determined the long-range fractal correlations by using detrended fluctuation analysis. Electrophysiologically, the baseline corrected field potential durations (cFPDs) were more prolonged in LQT-CMs than in wildtype (WT)-CMs. Bisoprolol did not have significant effects to the cFPD in any CMs. ML277 shortened cFPD in a dose-dependent fashion by 11 % and 5–11 % in WT- and LQT-CMs, respectively. JNJ303 prolonged cFPD in a dose-dependent fashion by 22 % and 7–13 % in WT- and LQT-CMs, respectively. At baseline, all CMs showed fractal correlations as determined by short-term scaling exponent α. However, in all CMs, the α was increased when pharmacological compounds were applied indicating of breakdown of fractal complexity. These findings suggest that the intrinsic mechanisms contributing to the fractal complexity are not altered in LQT-CMs. The modulation of I_{Ks} channel and β1-adrenoreceptors by pharmacological compounds may affect the fractal complexity of the hiPSC-CMs.

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Estimation of optimal matching position for orthogonal kV setup images and minimal setup margins in radiotherapy of whole breast and lymph node areas

Aim: The aim was to find an optimal setup image matching position and minimal setup margins to maximally spare the organs at risk in breast radiotherapy. Background: Radiotherapy of breast cancer is a routine task but has many challenges. We investigated residual position errors in whole breast radiotherapy when orthogonal setup images were

matched to different bony landmarks. Materials and methods: A total of 1111 orthogonal setup image pairs and tangential field images were analyzed retrospectively for 50 consecutive patients. Residual errors in the treatment field images were determined by matching the orthogonal setup images to the vertebrae, sternum, ribs and their compromises. The most important region was the chest wall as it is crucial for the dose delivered to the heart and the ipsilateral lung. Inter-observer variation in online image matching was investigated. Results: The best general image matching position was the compromise of the vertebrae, ribs and sternum, while the worst position was the vertebrae alone ($p \leq 0.03$). The setup margins required for the chest wall varied from 4.3 mm to 5.5 mm in the lung direction while in the superior-inferior (SI) direction the margins varied from 5.1 mm to 7.6 mm. The inter-observer variation increased the minimal margins by approximately 1 mm. The margin of the lymph node areas should be at least 4.8 mm. Conclusions: Setup margins can be reduced by proper selection of a matching position for the orthogonal setup images. To retain the minimal margins sufficient, systematic error of the chest wall should not exceed 4. mm in the tangential field image.

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Fine-mapping the 2q37 and 17q11.2-q22 loci for novel genes and sequence variants associated with a genetic predisposition to prostate cancer
The 2q37 and 17q12-q22 loci are linked to an increased prostate cancer (PrCa) risk. No candidate gene has been localized at 2q37 and the HOXB13 variant G84E only partially explains the linkage to 17q21-q22 observed in Finland. We screened these regions by targeted DNA sequencing to search for cancer-associated variants. Altogether, four novel susceptibility alleles were identified. Two ZNF652 (17q21.3) variants, rs116890317 and rs79670217, increased the risk of both sporadic and hereditary PrCa (rs116890317: OR = 3.3-7.8, $p = 0.003\text{-}3.3 \times 10^{-5}$; rs79670217: OR = 1.6-1.9, p = 0.002-0.009). The HDAC4 (2q37.2) variant rs73000144 (OR = 14.6, p = 0.018) and the EFCAB13 (17q21.3) variant rs118004742 (OR = 1.8, p = 0.048) were overrepresented in patients with familial PrCa. To map the variants within 2q37 and 17q11.2-q22 that may regulate PrCa-associated genes, we combined DNA sequencing results with transcriptome data obtained by RNA sequencing. This expression quantitative trait locus (eQTL) analysis identified 272 single-nucleotide polymorphisms (SNPs) possibly regulating six genes that were differentially expressed between cases and controls. In a modified approach, prefiltered PrCa-associated SNPs were exploited and interestingly, a novel eQTL targeting ZNF652 was identified. The novel variants identified in this study could be utilized for PrCa risk assessment, and they further validate the suggested role of ZNF652 as a PrCa candidate gene. The regulatory regions discovered by eQTL mapping increase our understanding of the relationship between regulation of gene expression and susceptibility to PrCa and provide a valuable starting point for future functional research.

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Contributors: Laitinen, V. H., Rantapero, T., Fischer, D., Vuorinen, E. M., Tammela, T. L. J., Wahlfors, T., Schleutker, J.

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Research output: Contribution to journal › Article › Scientific › peer-review

Incidence trends of vestibular schwannomas in Denmark, Finland, Norway and Sweden in 1987-2007
Methods:Comprehensive data were available from all registries only for the period from 1987 to 2007. An analysis of a longer time period (1965-2007) was conducted with the Norwegian and Swedish data. Results: The average age-standardised incidence rates during 1987-2007 varied from 6.1 per 1 000 000 person-years (95% confidence interval (CI), 5.4-6.7) among Finnish men to 11.6 (95% CI, 10.4-12.7) in Danish men, and from 6.4 per 1 000 000 person-years (95% CI, 5.7-7.0) among Swedish women to 11.6 (95% CI, 10.5-12.8) among Danish women. An overall annual increase of 3.0% (95% CI 2.1-3.9) was observed when all countries and both sexes were combined, with considerable differences between countries. However, the practices of both reporting and coding VS cases varied markedly between countries and over time, which poses a challenge for interpretation of the results. Conclusion: The overall incidence of VS increased in all the four Nordic countries combined between 1987 and 2007, with marked differences between countries. However, the incidence rates more or less stabilised in the late 1990s, showing relatively constant incidence rates and even some decline after 2000.

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Organisations: Prostate cancer research center (PCRC), Tampere School of Public Health, Karolinska Institutet, Finnish Cancer Registry, Danish Cancer Society Research Center, Cancer Registry of Norway Institute of Population-Based Cancer Research, STUK - Radiation and Nuclear Safety Authority
Contributors: Larjavaara, S., Feychting, M., Sankila, R., Johansen, C., Klaeboe, L., Schüz, J., Auvinen, A.
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Proteasome inhibitors induce nucleolar aggregation of proteasome target proteins and polyadenylated RNA by altering ubiquitin availability

The ubiquitin-proteasome pathway is essential for most cellular processes, including protein quality control, cell cycle, transcription, signaling, protein transport, DNA repair and stress responses. Hampered proteasome activity leads to the accumulation of polyubiquitylated proteins, endoplastic reticulum (ER) stress and even cell death. The ability of chemical proteasome inhibitors (PIs) to induce apoptosis is utilized in cancer therapy. During PI treatment, misfolded proteins accrue to cytoplasmic aggresomes. The formation of aggresome-like structures in the nucleus has remained obscure. We identify here a nucleolus-associated RNA-protein aggregate (NoA) formed by the inhibition of proteasome activity in mammalian cells. The aggregate forms within the nucleolus and is dependent on nucleolar integrity, yet is a separate structure, lacking nucleolar marker proteins, ribosomal RNA (rRNA) and rRNA synthesis activity. The NoAs contain polyadenylated RNA, conjugated ubiquitin and numerous nucleoplasmic proteasome target proteins. Several of these are key factors in oncogenesis, including transcription factors p53 and retinoblastoma protein (Rb), several cell cycle-regulating cyclins and cyclin-dependent kinases (CDKs), and stress response kinases ataxia-telangiectasia mutated (ATM) and Chk1. The aggregate formation depends on ubiquitin availability, as shown by modulating the levels of ubiquitin and deubiquitinases. Furthermore, inhibition of chromosome region maintenance 1 protein homolog (CRM1) export pathway aggravates the formation of NoAs. Taken together, we identify here a novel nuclear stress body, which forms upon proteasome inactivity within the nucleolus and is detectable in mammalian cell lines and in human tissue. These findings show that the nucleolus controls protein and RNA surveillance and export by the ubiquitin pathway in a previously unidentified manner, and provide mechanistic insight into the cellular effects of PIs.

General information

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Organisations: Prostate cancer research center (PCRC), University of Tampere Institute of Medical Technology, Haartman Institute, Johns Hopkins School of Medicine
Contributors: Latonen, L., Moore, H. M., Bai, B., Jäämaa, S., Laiho, M.
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The diverse role of miR-31 in regulating cancer associated phenotypes

In the past 10 years research on miRNAs has demonstrated their central role in regulating gene expression both in normal and diseased tissue. The expression of miRNAs is widely altered in cancer, leading to abnormal expression of the genes regulated by these miRNAs, and subsequently alterations in entire molecular networks and pathways. One especially interesting cancer-related miRNA is miR-31 which is frequently altered in a large variety of cancers. The functional role of miR-31 is extremely complex and miR-31 can hold both tumor suppressive and oncogenic roles in different tumor types. The phenotype caused by aberrant miR-31 expression seems to be strongly dependent on the endogenous expression levels. For example, in breast cancer loss of miR-31 expression is associated with high risk of metastases, whereas in colorectal cancer high miR-31 expression correlates with advanced disease stage. This review summarizes the complex expression patterns of miR-31 in human cancers, describes the variable phenotypes caused by altered miR-31 expression, and highlights the current knowledge on the genes targeted by miR-31.

General information

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Contributors: Laurila, E. M., Kallioniemi, A.
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Research output: Contribution to journal › Article › Scientific › peer-review

Effects of aerobic and strength training on aerobic capacity, muscle strength, and gene expression of lymphomonocytes in patients with stable CAD
This study examined the effectiveness, suitability, and safety of a mixed interval-type aerobic and strength training program (MIAST) on physical fitness in patients with stable coronary artery disease (CAD) without history of myocardial infarction (MI). Twenty-three patients with stable CAD were randomly assigned to a MIAST (n = 12; mean age 58.6 years) or control (n = 11; 63.3 years) group. The MIAST group participated in the progressive training program twice a week for 21 weeks. Peak oxygen uptake (VO_{2peak}), workload, and exercise time were measured as were maximal muscle strength, serum lipids, glucose concentration, and the cross-sectional area (CSA) of knee extensors. The safety and suitability of the program were assessed by wireless electrocardiogram (ECG) monitoring and exercise diaries. VO_{2peak} (6.9%; $P < 0.05$) and exercise time (11.2%; $P < 0.05$) improved significantly after 12 weeks of training in the MIAST group compared to the control group. Muscle strength (19.9%; $P < 0.05$) and CSA (2.2%; $P < 0.05$) increased, and serum lipids and blood glucose tended to decrease after the training. The successful training program (increase in maximal oxygen uptake) increased the gene expression of oxygen metabolism and decreased the gene expression of inflammation pathways in lymphomonocytes. The MIAST program, including interval-type aerobic and strength training, was safe, did not cause any adverse effects, and led to significant improvements in physical fitness in patients with stable CAD.

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Contributors: Lehti, M., Valkeinen, H., Sipilä, S., Perhonen, M., Rottensteiner, M., Pullinen, T., Pietiläinen, R., Nyman, K., Vehkaoja, A., Kainulainen, H., Kujala, U. M.
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Research output: Contribution to journal › Article › Scientific › peer-review

Clinical association analysis of ependymomas and pilocytic astrocytomas reveals elevated FGFR3 and FGFR1 expression in aggressive ependymomas

Background: Fibroblast growth factor receptors (FGFRs) are well-known proto-oncogenes in several human malignancies and are currently therapeutically targeted in clinical trials. Among glioma subtypes, activating FGFR1 alterations have been observed in a subpopulation of pilocytic astrocytomas while FGFR3 fusions occur in IDH wild-type diffuse gliomas, resulting in high FGFR3 protein expression. The purpose of this study was to associate FGFR1 and FGFR3 protein levels with clinical features and genetic alterations in ependymoma and pilocytic astrocytoma. Methods: FGFR1 and FGFR3 expression levels were detected in ependymoma and pilocytic astrocytoma tissues using immunohistochemistry. Selected cases were further analyzed using targeted sequencing. Results: Expression of both FGFR1 and FGFR3 varied within all tumor types. In ependymomas, increased FGFR3 or FGFR1 expression was associated with high tumor grade, cerebral location, young patient age, and poor prognosis. Moderate-to-strong expression of FGFR1 and/or FGFR3 was observed in 76% of cerebral ependymomas. Cases with moderate-to-strong expression of both proteins had poor clinical prognosis. In pilocytic astrocytomas, moderate-to-strong FGFR3 expression was detected predominantly in non-pediatric patients. Targeted sequencing of 12 tumors found no protein-altering mutations or fusions in FGFR1 or FGFR3. Conclusions: Elevated FGFR3 and FGFR1 protein expression is common in aggressive ependymomas but likely not driven by genetic alterations. Further studies are warranted to evaluate whether ependymoma patients with high FGFR3 and/or FGFR1 expression could benefit from treatment with FGFR inhibitor based therapeutic approaches currently under evaluation in clinical trials.

General information

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Organisations: BioMediTech, Faculty of Biomedical Sciences and Engineering, Research group: Computational Systems Biology, Signal Processing, BioMediTech, Tampere University Hospital, Comprehensive Cancer Center of Wake Forest Baptist Medical Center
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EXT="Annala, Matti"
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Intragenic rearrangement and altered RNA splicing of the androgen receptor in a cell-based model of prostate cancer progression

Androgen depletion for advanced prostate cancer (PCa) targets activity of the androgen receptor (AR), a steroid receptor transcription factor required for PCa growth. The emergence of lethal castration-resistant PCa (CRPCa) is marked by

aberrant reactivation of the AR despite ongoing androgen depletion. Recently, alternative splicing has been described as a mechanism giving rise to COOH-terminally truncated, constitutively active AR isoforms that can support the CRPCa phenotype. However, the pathologic origin of these truncated AR isoforms is unknown. The goal of this study was to investigate alterations in AR expression arising in a cell-based model of PCa progression driven by truncated AR isoform activity. We show that stable, high-level expression of truncated AR isoforms in 22Rv1 CRPCa cells is associated with intragenic rearrangement of an approximately 35-kb AR genomic segment harboring a cluster of previously described alternative AR exons. Analysis of genomic data from clinical specimens indicated that related AR intragenic copy number alterations occurred in CRPCa in the context of AR amplification. Cloning of the break fusion junction in 22Rv1 cells revealed long interspersed nuclear elements (LINE-1) flanking the rearranged segment and a DNA repair signature consistent with microhomology-mediated, break-induced replication. This rearrangement served as a marker for the emergence of a rare subpopulation of CRPCa cells expressing high levels of truncated AR isoforms during PCa progression in vitro. Together, these data provide the first report of AR intragenic rearrangements in CRPCa and an association with pathologic expression of truncated AR isoforms in a cell-based model of PCa progression.

General information
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Contributors: Li, Y., Alsagabi, M., Fan, D., Bova, G. S., Tewfik, A. H., Dehm, S. M.
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Source ID: 79952772097
Research output: Contribution to journal › Article › Scientific › peer-review

Genetic markers associated with early cancer-specific mortality following prostatectomy
BACKGROUND This study sought to identify novel effectors and markers of localized but potentially life-threatening prostate cancer (PCa), by evaluating chromosomal copy number alterations (CNAs) in tumors from patients who underwent prostatectomy and correlating these with clinicopathologic features and outcome. METHODS CNAs in tumor DNA samples from 125 patients in the discovery cohort who underwent prostatectomy were assayed with high-resolution Affymetrix 6.0 single-nucleotide polymorphism microarrays and then analyzed using the Genomic Identification of Significant Targets in Cancer (GISTIC) algorithm. RESULTS The assays revealed 20 significant regions of CNAs, 4 of them novel, and identified the target genes of 4 of the alterations. By univariate analysis, 7 CNAs were significantly associated with early PCa-specific mortality. These included gains of chromosomal regions that contain the genes MYC, ADAR, or TPD52 and losses of sequences that incorporate SERPINB5, USP10, PTEN, or TP53. On multivariate analysis, only the CNAs of PTEN (phosphatase and tensin homolog) and MYC (v-myc myelocytomatosis viral oncogene homolog) contributed additional prognostic information independent of that provided by pathologic stage, Gleason score, and initial prostate-specific antigen level. Patients whose tumors had alterations of both genes had a markedly elevated risk of PCa-specific mortality (odds ratio = 53; 95% CI = 6.92-405, $P = 1 \times 10^{-4}$). Analyses of 333 tumors from 3 additional distinct patient cohorts confirmed the relationship between CNAs of PTEN and MYC and lethal PCa. CONCLUSIONS This study identified new CNAs and genes that likely contribute to the pathogenesis of localized PCa and suggests that patients whose tumors have acquired CNAs of PTEN, MYC, or both have an increased risk of early PCa-specific mortality.

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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Wake Forest University School of Medicine, Karolinska Institutet , Karolinska University Hospital, University of California San Diego, School of Medicine, Johns Hopkins Medical Institutions

Contributors: Liu, W., Xie, C. C., Thomas, C. Y., Kim, S. T., Lindberg, J., Egevad, L., Wang, Z., Zhang, Z., Sun, J., Sun, J. , Koty, P. P., Kader, A. K., Cramer, S. D., Bova, G. S., Zheng, S. L., Grönberg, H., Isaacs, W. B., Xu, J.
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Source ID: 84879088895
Research output: Contribution to journal › Article › Scientific › peer-review

Identification of novel CHD1-associated collaborative alterations of genomic structure and functional assessment of CHD1 in prostate cancer
A clearer definition of the molecular determinants that drive the development and progression of prostate cancer (PCa) is urgently needed. Efforts to map recurrent somatic deletions in the tumor genome, especially homozygous deletions (HODs), have provided important positional information in the search for cancer-causing genes. Analyzing HODs in the tumors of 244 patients from two independent cohorts and 22 PCa xenografts using high-resolution single-nucleotide polymorphism arrays, herein we report the identification of CHD1, a chromatin remodeler, as one of the most frequently homozygously deleted genes in PCa, second only to PTEN in this regard. The HODs observed in CHD1, including deletions affecting only internal exons of CHD1, were found to completely extinguish the expression of mRNA of this gene in PCa xenografts. Loss of this chromatin remodeler in clinical specimens is significantly associated with an increased number of additional chromosomal deletions, both hemi-and homozygous, especially on 2q, 5q and 6q. Together with the deletions observed in HEK293 cells stably transfected with CHD1 small hairpin RNA, these data suggest a causal relationship. Downregulation of Chd1 in mouse prostate epithelial cells caused dramatic morphological changes indicative of increased invasiveness, but did not result in transformation. Indicating a new role of CHD1, these findings collectively suggest that distinct CHD1-associated alterations of genomic structure evolve during and are required for the development of PCa.

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Contributors: Liu, W., Lindberg, J., Sui, G., Luo, J., Egevad, L., Li, T., Xie, C., Wan, M., Kim, S. T., Wang, Z., Turner, A. R. , Zhang, Z., Feng, J., Yan, Y., Sun, J., Bova, G. S., Ewing, C. M., Yan, G., Gielzak, M., Cramer, S. D., Vessella, R. L., Zheng, S. L., Grönberg, H., Isaacs, W. B., Xu, J.
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Source: Scopus
Source ID: 84865639773
Research output: Contribution to journal › Article › Scientific › peer-review

Somatic mutation profiling and associations with prognosis and trastuzumab benefit in early breast cancer

Background Certain somatic alterations in breast cancer can define prognosis and response to therapy. This study investigated the frequencies, prognostic effects, and predictive effects of known cancer somatic mutations using a randomized, adjuvant, phase III clinical trial dataset. Methods The FinHER trial was a phase III, randomized adjuvant breast cancer trial involving 1010 women. Patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer were further randomized to 9 weeks of trastuzumab or no trastuzumab. Seven hundred five of 1010 tumors had sufficient DNA for genotyping of 70 somatic hotspot mutations in 20 genes using mass spectrometry. Distant disease-free survival (DDFS), overall survival (OS), and interactions with trastuzumab were explored with Kaplan-Meier and Cox regression analyses. All statistical tests were two-sided. Results Median follow-up was 62 months. Of 705 tumors, 687 were successfully genotyped. PIK3CA mutations (exons 1, 2, 4, 9, 13, 18, and 20) were present in 25.3% (174 of 687) and TP53 mutations in 10.2% (70 of 687). Few other mutations were found: three ERBB2 and single cases of KRAS, ALK, STK11/LKB1, and AKT2. PIK3CA mutations were associated with estrogen receptor positivity (P interaction: DDFS P =. 14; OS P =. 24). Conclusions In this dataset, targeted genotyping revealed only two alterations at a frequency greater than 10%, with other mutations observed infrequently. PIK3CA mutations were associated with a better outcome, however this effect disappeared after 3 years. There were no statistically significant associations with trastuzumab benefit.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Université Libre de Bruxelles, Breast Cancer Translational Research Laboratory J-C Heuson, Institut Jules Bordet, Bld de Waterloo, KU Leuven, Tampere University Hospital, Helsinki University Central Hospital, University Central Hospital Kuopio
Contributors: Loi, S., Michiels, S., Lambrechts, D., Fumagalli, D., Claes, B., Kellokumpu-Lehtinen, P. L., Bono, P., Kataja, V., Piccart, M. J., Joensuu, H., Sotiriou, C.
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Impact of epoetin-beta on anemia and health-related quality of life in cancer patients: A prospective observational study using the generic 15D instrument

Aim: Cancer-related anemia has a negative impact on the health-related quality of life (HRQoL). Our aim was to evaluate prospectively the effect of treatment of anemia with an erythropoietin on the hemoglobin level and HRQoL in cancer patients with anemia. Patients and Methods: Consecutive patients (N=114) treated for the first time with epoetin (epoetin beta 30000 IU/wk, NeoRecormon®) for anemia during cancer treatment were eligible for study inclusion. Baseline characteristics were collected from patients' records. HRQoL was measured by the generic 15D instrument and fatigue by visual analogue scale (VAS) at baseline and four months from the start of the treatment with epoetin. The majority (87%)

of patients had solid tumors; 69% with a metastatic disease and 89% disease with comorbidities. Results: The mean hemoglobin concentration (SD) in blood increased from 96.6 (8.9) g/L to 112.9 (21.2) g/L, by 16.5 (20.6) g/L (p

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Oulu University Hospital, Department of Pulmonology, Ita-Suomen yliopisto, Turku University Hospital, Helsinki University Central Hospital, Tampere University Hospital
Contributors: Mäenpa, J., Puistola, U., Riska, H., Sintonen, H., Saarni, O., Juvonen, E., Kellokumpu-Lehtinen, P. L.
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Research output: Contribution to journal › Article › Scientific › peer-review

A Comparative View on Easy to Deploy non-Integrating Methods for Patient-Specific iPSC Production

Induced pluripotent stem cells (iPSCs) are routinely produced from dermal fibroblasts, with potential applications ranging from in vitro disease models to drug discovery and regenerative medicine. The need of eliminating the remaining reprogramming factors after iPSC production spurred the development of non-integrating viruses such as Sendai and other methods to deliver episomal vectors, which are progressively lost upon cell division. We compared four widespread methods (Sendai virus, Nucleofector, Neon transfection system and Lipofectamine 3000) to generate integration-free iPSC lines from primary human dermal fibroblasts (hDF) of three patients. Furthermore, we performed extensive characterization of the iPSC lines. We were able to produce iPSC lines with all tested methods with variable efficiency. Sendai virus method achieved the overall highest reprogramming rate, followed by electroporation-based methods Nucleofector and Neon transfection systems. Chemical-based Lipofectamine 3000 delivery resulted in the lowest number of iPSC colonies. We found the reprogramming rate to be intrinsically dependent on the individual hDFs but the amenability of each hDF to reprogramming showed consistency between methods. Regardless of the reprogramming strategy, iPSCs obtained did not reveal any significant differences in their morphology, expression of pluripotency markers, EB formation, karyotype or gene expression profiles.

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Università degli Studi di Milano, Tampere University Hospital
Contributors: Manzini, S., Viiri, L. E., Marttila, S., Aalto-Setälä, K.
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Research output: Contribution to journal › Article › Scientific › peer-review

Diagnostic and prognostic signatures from the small non-coding RNA transcriptome in prostate cancer
Prostate cancer (PCa) is the most frequent male malignancy and the second most common cause of cancer-related death in Western countries. Current clinical and pathological methods are limited in the prediction of postoperative outcome. It is becoming increasingly evident that small non-coding RNA (ncRNA) species are associated with the development and progression of this malignancy. To assess the diversity and abundance of small ncRNAs in PCa, we analyzed the composition of the entire small transcriptome by Illumina/Solexa deep sequencing. We further analyzed the microRNA (miRNA) expression signatures of 102 fresh-frozen patient samples during PCa progression by miRNA microarrays. Both platforms were cross-validated by quantitative reverse transcriptase-PCR. Besides the altered expression of several miRNAs, our deep sequencing analyses revealed strong differential expression of small nucleolar RNAs (snoRNAs) and transfer RNAs (tRNAs). From microarray analysis, we derived a miRNA diagnostic classifier that accurately distinguishes normal from cancer samples. Furthermore, we were able to construct a PCa prognostic predictor that independently forecasts postoperative outcome. Importantly, the majority of miRNAs included in the predictor also exhibit high sequence counts and concordant differential expression in Illumina PCa samples, supported by quantitative reverse transcriptase-PCR. Our findings provide miRNA expression signatures that may serve as an accurate tool for the diagnosis and prognosis of PCa.

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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Josephine Nefkens Institute - JNI, University of Tampere Institute of Medical Technology, Exiqon A/S
Contributors: Martens-Uzunova, E. S., Jalava, S. E., Dits, N. F., Van Leenders, G. J. L. H., Møller, S., Trapman, J., Bangma, C. H., Litman, T., Visakorpi, T., Jenster, G.
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Keywords: deep sequencing, microarray, microRNA, prostate cancer, Q-PCR, snoRNA
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Source ID: 84857372726
Research output: Contribution to journal › Article › Scientific › peer-review

NMD and microRNA expression profiling of the HPCX1 locus reveal MAGEC1 as a candidate prostate cancer predisposition gene
Background: Several predisposition loci for hereditary prostate cancer (HPC) have been suggested, including HPCX1 at Xq27-q28, but due to the complex structure of the region, the susceptibility gene has not yet been identified.Methods: In this study, nonsense-mediated mRNA decay (NMD) inhibition was used for the discovery of truncating mutations. Six prostate cancer (PC) patients and their healthy brothers were selected from a group of HPCX1-linked families. Expression analyses were done using Agilent 44 K oligoarrays, and selected genes were screened for mutations by direct sequencing. In addition, microRNA expression levels in the lymphoblastic cells were analyzed to trace variants that might

alter miRNA expression and explain partly an inherited genetic predisposion to PC.Results: Seventeen genes were selected for resequencing based on the NMD array, but no truncating mutations were found. The most interesting variant was MAGEC1 p.Met1?. An association was seen between the variant and unselected PC (OR = 2.35, 95% CI = 1.10-5.02) and HPC (OR = 3.38, 95% CI = 1.10-10.40). miRNA analysis revealed altogether 29 miRNAs with altered expression between the PC cases and controls. miRNA target analysis revealed that 12 of them also had possible target sites in the MAGEC1 gene. These miRNAs were selected for validation process including four miRNAs located in the X chromosome. The expressions of 14 miRNAs were validated in families that contributed to the significant signal differences in Agilent arrays.Conclusions: Further functional studies are needed to fully understand the possible contribution of these miRNAs and MAGEC1 start codon variant to PC.

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Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Pirkanmaan sairaanhoitopiiri, School of Health Sciences, University of Tampere, Medical School
Contributors: Mattila, H., Schindler, M., Isotalo, J., Ikonen, T., Vihinen, M., Oja, H., Tammela, T. L., Wahlfors, T., Schleutker, J.
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Research output: Contribution to journal › Article › Scientific › peer-review

European Code against Cancer 4th Edition: Ionising and non-ionising radiation and cancer
Ionising radiation can transfer sufficient energy to ionise molecules, and this can lead to chemical changes, including DNA damage in cells. Key evidence for the carcinogenicity of ionising radiation comes from: follow-up studies of the survivors of the atomic bombings in Japan; other epidemiological studies of groups that have been exposed to radiation from medical, occupational or environmental sources; experimental animal studies; and studies of cellular responses to radiation. Considering exposure to environmental ionising radiation, inhalation of naturally occurring radon is the major source of radiation in the population – in doses orders of magnitude higher than those from nuclear power production or nuclear fallout. Indoor exposure to radon and its decay products is an important cause of lung cancer; radon may cause approximately one in ten lung cancers in Europe. Exposures to radon in buildings can be reduced via a three-step process of identifying those with potentially elevated radon levels, measuring radon levels, and reducing exposure by installation of remediation systems. In the 4th Edition of the European Code against Cancer it is therefore recommended to: “Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels”. Non-ionising types of radiation (those with insufficient energy to ionise molecules) – including extremely low-frequency electric and magnetic fields as well as radiofrequency electromagnetic fields – are not an established cause of cancer and are therefore not addressed in the recommendations to reduce cancer risk.

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Organisations: Prostate cancer research center (PCRC), Public Health England, STUK - Radiation and Nuclear Safety Authority, International Agency for Research on Cancer, Erasmus University Medical Center, Elbekliniken Stade/Buxtehude
Contributors: McColl, N., Auvinen, A., Kesminiene, A., Espina, C., Erdmann, F., de Vries, E., Greinert, R., Harrison, J., Schüz, J.
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Research output: Contribution to journal › Article › Scientific › peer-review

Detection of Pancreatic Cancer by Urine Volatile Organic Compound Analysis
BACKGROUND/AIM: Most pancreatic cancer patients are diagnosed at an advanced stage, since the diagnosis is demanding. Field asymmetric waveform ion mobility spectrometry (FAIMS) is a sensitive technique used for the detection of volatile organic compounds (VOC). We evaluated the ability of FAIMS to discriminate between pancreatic cancer and healthy controls from a urine sample. PATIENTS AND METHODS: For a proof-of-concept study in three Finnish hospitals, 68 patients with pancreatic cancer, 36 with acute pancreatitis, 18 with chronic pancreatitis, 8 with pancreatic pre-malign lesions and 52 healthy controls were prospectively recruited. Urine samples were collected at the time of diagnosis and stored at -70°C. The samples were subsequently measured with FAIMS. The data were processed with linear discriminant analysis and cross-validated with leave-one-out cross-validation. RESULTS: FAIMS distinguished pancreatic cancer from controls with a sensitivity of 79% and specificity of 79%. CONCLUSION: As a non-invasive and rapid urine test, FAIMS can discriminate patients with pancreatic cancer from healthy controls.

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Organisations: Faculty of Biomedical Sciences and Engineering, University of Eastern Finland, University Central Hospital Kuopio, Hatanpää Hospital, Central Hospital of Seinäjoki, Tampere University Hospital, Fimlab Laboratories Ltd, Finnish Cardiovascular Research Center
Contributors: Nissinen, S. I., Roine, A., Hokkinen, L., Karjalainen, M., Venäläinen, M., Helminen, H., Niemi, R., Lehtimäki, T., Rantanen, T., Oksala, N.
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Scopus rating (2019): CiteScore 3.3 SJR 0.716 SNIP 0.633
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Source ID: 85059243029
Research output: Contribution to journal › Article › Scientific › peer-review

Recurrent moderate-risk mutations in Finnish breast and ovarian cancer patients
Mutations in BRCA1 and BRCA2 genes predispose to breast and ovarian cancer (BC/OC) with a high lifetime risk, whereas mutations in PALB2, CHEK2, ATM, FANCM, RAD51C and RAD51D genes cause a moderately elevated risk. In the Finnish population, recurrent mutations have been identified in all of these genes, the latest being CHEK2 c.319+2T>A

and c.444+1G>A. By genotyping 3,156 cases and 2,089 controls, we estimated the frequencies of CHEK2 c.319+2T>A and c.444+1G>A in Finnish BC patients. CHEK2 c.319+2T>A was detected in 0.7% of the patients, and it was associated with a high risk of BC in the unselected patient group (OR = 5.40 [95% CI 1.58–18.45], p = 0.007) and similarly in the familial patient group. CHEK2 c.444+1G>A was identified in 0.1% of all patients. Additionally, we evaluated the combined prevalence of recurrent moderate-risk gene mutations in 2,487 BC patients, 556 OC patients and 261 BRCA1/2 carriers from 109 families. The overall frequency of the mutations was 13.3% in 1,141 BRCA1/2-negative familial BC patients, 7.5% in 1,727 unselected BC patients and 7.2% in 556 unselected OC patients. At least one moderate-risk gene mutation was found in 12.5% of BRCA1 families and 7.1% of BRCA1 index patients, as well as in 17.0% of BRCA2 families and 11.3% of BRCA2 index patients, and the mutations were associated with an additional risk in the BRCA1/2 index patients (OR = 2.63 [1.15–5.48], p = 0.011). These results support gene panel testing of even multiple members of BC families where several mutations may segregate in different individuals.

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Organisations: BioMediTech, Helsinki University Central Hospital, Turku University Hospital, University of Helsinki
Contributors: Nurmi, A., Muranen, T. A., Pelttari, L. M., Kiiski, J. I., Heikkinen, T., Lehto, S., Kallioniemi, A., Schleutker, J., Bützow, R., Blomqvist, C., Aittomäki, K., Nevanlinna, H.
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Fine mapping of 11q13.5 identifies regions associated with prostate cancer and prostate cancer death

Background Chromosomal region 11q13-14 associates with prostate cancer (PrCa). Previously, we identified a rare intronic mutation on EMSY (11q13.5) that increases the risk of aggressive PrCa and associates with familial PrCa. Here, we further study the genetic structure and variants of the PrCa susceptibility region 11q13.5. Methods This study included 2716 unselected hospital-based PrCa cases, 1318 cases of a screening trial and 908 controls of Finnish origin. We imputed single nucleotide polymorphisms (SNPs) and structural variants from the 1000 Genomes Project and validated the associations of the variants in two PrCa patient sets by genotyping. Genetic structure was studied with haplotype analysis. Results Two independent regions at 11q13.5 were associated with PrCa risk. The most significant association was at EMSY (rs10899221, odds ratio (OR) 1.29-1.40, $P = 3.5 \times 10^{-4}$-0.002) near the previously identified mutation. Correlated intronic SNPs rs10899221 and rs72944758 formed with other EMSY variants common and rare haplotypes that were associated with increased risk ($P = 4.0 \times 10^{-4}$) and decreased risk (P = 0.01) of PrCa, respectively. The other associated region was intergenic. Among the six validated variants, rs12277366 was significant in both patient sets (OR 1.15-1.17, P = 0.01). Haplotypes associated with an increased risk (P = 0.02) and a decreased risk (P = 0.02) were identified. In addition, the intergenic region was strongly associated with PrCa death, with the most significant association at rs12277366 (OR = 0.72, $P = 4.8 \times 10^{-5}$). Conclusions These findings indicate that 11q13.5 contributes to PrCa predisposition with complex genetic structure and is associated with PrCa death.

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Organisations: Prostate cancer research center (PCRC), School of Management (JKK), University of Helsinki, Turun Yliopisto/Turun Biomateriaalikeskus
Contributors: Nurminen, R., Lehtonen, R., Auvinen, A., Tammela, T. L. J., Wahlfors, T., Schleutker, J.
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Keywords: Death, EMSY, Genetic association study, Prostate cancer, Single nucleotide polymorphism
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Research output: Contribution to journal › Article › Scientific › peer-review

Identification of an aggressive prostate cancer predisposing variant at 11q13
Prostate cancer is the most frequently diagnosed cancer in men; however, the genetic basis of susceptibility remains elusive. The EMSY gene is located in the prostate cancer linked chromosome region at 11q13.5. The aim of this study was to screen EMSY for sequence variants and to evaluate its association with the risk of prostate cancer. We performed a Finnish population-based case-control study with 923 controls, 184 familial prostate cancer cases and 2,301 unselected prostate cancer cases. Variants were screened using sequencing and validated using the TaqMan assay and High Resolution Melting analysis. A total of 27 sequence variants were found, and 17 of them were novel. A rare intronic variant, IVS6-43A>G (minor allele frequency of 0.004), increased the prostate cancer risk in familial cases (odds ratio [OR] = 7.5; 95% confidence interval [CI] = 1.3-45.5; p = 0.02). Further analysis with clinicopathological data revealed that the variant is associated with aggressive unselected cases (prostate specific antigen ≤yen; 20 μg/L or Gleason grade ≤yen; 7), based on both case-control (OR = 6.0; 95% CI = 1.3-26.4; p = 0.03) and case-case analyses (OR = 6.5; 95% CI = 1.5-28.4; p = 0.002). In addition, all variant-positive familial cases had aggressive cancer. Our results indicate that the intronic variant IVS6-43A>G increases the familial and unselected prostate cancer risk in a Finnish population and contributes to the aggressive progression of the disease in a high-penetrance manner. The potential role of the variant as a predictive genetic marker for aggressive prostate cancer should be further evaluated.

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Contributors: Nurminen, R., Wahlfors, T., Tammela, T. L., Schleutker, J.
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Source: Scopus
Source ID: 79958021225
Research output: Contribution to journal › Article › Scientific › peer-review

Reducing overdiagnosis by polygenic risk-stratified screening: Findings from the Finnish section of the ERSPC

Background:We derived estimates of overdiagnosis by polygenic risk groups and examined whether polygenic risk-stratified screening for prostate cancer reduces overdiagnosis.Methods:We calculated the polygenic risk score based on genotypes of 66 known prostate cancer loci for 4967 men from the Finnish section of the European Randomised Study of Screening for Prostate Cancer. We stratified the 72 072 men in the trial into those with polygenic risk below and above the median. Using a maximum likelihood method based on interval cancers, we estimated the mean sojourn time (MST) and episode sensitivity. For each polygenic risk group, we estimated the proportion of screen-detected cancers that are likely to be overdiagnosed from the difference between the observed and expected number of screen-detected cancers.Results:Of the prostate cancers, 74% occurred among men with polygenic risk above population median. The sensitivity was 0.55 (95% confidence interval (CI) 0.45-0.65) and MST 6.3 (95% CI 4.2-8.3) years. The overall overdiagnosis was 42% (95% CI 37-52) of the screen-detected cancers, with 58% (95% CI 54-65) in men with the lower and 37% (95% CI 31-47) in those with higher polygenic risk.Conclusion:Targeting screening to men at higher polygenic risk could reduce the proportion of cancers overdiagnosed.

General information

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Organisations: Prostate cancer research center (PCRC), University College London, University of Cambridge, Turun Yliopisto/Turun Biomateriaalikeskus, Finnish Cancer Registry, Tampere University Hospital, Royal Marsden NHS Foundation Trust, Queen Mary University of London
Contributors: Pashayan, N., Pharoah, P. D. P., Schleutker, J., Talala, K., Tammela, T. L. J., Määttänen, L., Harrington, P., Tyrer, J., Eeles, R., Duffy, S. W., Auvinen, A.
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Research output: Contribution to journal › Article › Scientific › peer-review

Quality of life of recently treated patients with breast cancer

Aim: To investigate whether the negative quality of life result of a large randomized exercise intervention study (BREX) was due to considerable spontaneous recovery after adjuvant treatments. Patients and Methods: The change in QoL was studied in the control patients of the BREX study (Group 1) and a group of similar follow-up patients that did not participate in any intervention study (Group 2). QoL was measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 with the breast cancer module supplement 6 and 12 months after surgery. Results: QoL improved in both groups between 6 and 12 months after surgery. The improvement was similar in both groups for global QoL and for most of the QoL sub-scales. Conclusion: No evidence was found to support the hypothesis that participation in an exercise intervention per se significantly improves QoL. Spontaneous improvement in QoL began during the first six months after the primary treatments, which might have confounded the results of the intervention of the BREX study.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Helsinki University Central Hospital, Helsinki and Uusimaa Hospital Group, Tampere University Hospital, Turku University Hospital, Central Finland Central Hospital, Medcare Foundation, Society of Swedish Literature in Finland

Contributors: Penttinen, H., Rautalin, M., Roine, R., Jahkola, T., Kellokumpu-Lehtinen, P. L., Huovinen, R., Kautiainen, H., Järvenpää, S., Hakamies-Blomqvist, L., Blomqvist, C., Saarto, T.
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ASJC Scopus subject areas: Cancer Research, Oncology
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Research output: Contribution to journal › Article › Scientific › peer-review

Cancer incidence among Nordic airline cabin crew
Airline cabin crew are occupationally exposed to cosmic radiation and jet lag with potential disruption of circadian rhythms. This study assesses the influence of work-related factors in cancer incidence of cabin crew members. A cohort of 8,507 female and 1,559 male airline cabin attendants from Finland, Iceland, Norway and Sweden was followed for cancer incidence for a mean follow-up time of 23.6 years through the national cancer registries. Standardized incidence ratios (SIRs) were defined as ratios of observed and expected numbers of cases. A case-control study nested in the cohort (excluding Norway) was conducted to assess the relation between the estimated cumulative cosmic radiation dose and cumulative number of flights crossing six time zones (indicator of circadian disruption) and cancer risk. Analysis of breast cancer was adjusted for parity and age at first live birth. Among female cabin crew, a significantly increased incidence was observed for breast cancer [SIR 1.50, 95% confidence interval (95% CI) 1.32-1.69], leukemia (1.89, 95% CI 1.03-3.17) and skin melanoma (1.85, 95% CI 1.41-2.38). Among men, significant excesses in skin melanoma (3.00, 95% CI 1.78-4.74), nonmelanoma skin cancer (2.47, 95% CI 1.18-4.53), Kaposi sarcoma (86.0, 95% CI 41.2-158) and alcohol-related cancers (combined SIR 3.12, 95% CI 1.95-4.72) were found. This large study with complete follow-up and comprehensive cancer incidence data shows an increased incidence of several cancers, but according to the case-control analysis, excesses appear not to be related to the cosmic radiation or circadian disruptions from crossing multiple time zones.

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Contributors: Pukkala, E., Helminen, M., Haldorsen, T., Hammar, N., Kojo, K., Linnersjö, A., Rafnsson, V., Tulinius, H., Tveten, U., Auvinen, A.
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Site-specific cancer risk in the Baltic cohort of Chernobyl cleanup workers, 1986-2007

Objective To assess site-specific cancer risk in the Baltic cohort of Chernobyl cleanup workers, 1986-2007. Methods The Baltic cohort includes 17,040 men from Estonia, Latvia and Lithuania who participated in the environmental cleanup after the accident at the Chernobyl Nuclear Power Station in 1986-1991 and who were followed up for cancer incidence until the end of 2007. Cancer cases diagnosed in the cohort and in the male population of each country were identified from the respective national cancer registers. The proportional incidence ratio (PIR) with 95% confidence interval (CI) was used to estimate the site-specific cancer risk in the cohort. For comparison and as it was possible, the site-specific standardised incidence ratio (SIR) was calculated for the Estonian sub-cohort, which was not feasible for the other countries. Results Overall, 756 cancer cases were reported during 1986-2007. A higher proportion of thyroid cancers in relation to the male population was found (PIR = 2.76; 95% CI 1.63-4.36), especially among those who started their mission shortly after the accident, in April-May 1986 (PIR = 6.38; 95% CI 2.34-13.89). Also, an excess of oesophageal cancers was noted (PIR = 1.52; 95% CI 1.06-2.11). No increased PIRs for leukaemia or radiation-related cancer sites combined were observed. PIRs and SIRs for the Estonian sub-cohort demonstrated the same site-specific cancer risk pattern. Conclusion Consistent evidence of an increase in radiation-related cancers in the Baltic cohort was not observed with the possible exception of thyroid cancer, where conclusions are hampered by known medical examination including thyroid screening among cleanup workers.

General information

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Contributors: Rahu, K., Hakulinen, T., Smailyte, G., Stengrevics, A., Auvinen, A., Inskip, P. D., Boice, J. D., Rahu, M.
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Research output: Contribution to journal › Article › Scientific › peer-review

Construction of therapeutically relevant human prostate epithelial fate map by utilising miRNA and mRNA microarray expression data

Background: Objective identification of key miRNAs from transcriptomic data is difficult owing to the inherent inconsistencies within miRNA target-prediction algorithms and the promiscuous nature of miRNA-mRNA target relationship. Methods: An integrated database of miRNAs and their 'relevant' mRNA targets was generated from validated miRNA and mRNA microarray data sets generated from patient-derived prostate epithelial normal and cancer stem-like cells (SCs) and committed basal (CB) cells. The effect of miR-542-5p inhibition was studied to provide proof-of-principle for database utility. Results: Integration of miRNA-mRNA databases showed that signalling pathways and processes can be regulated by a single or relatively few miRNAs, for example, DNA repair/Notch pathway by miR-542-5p, P=0.008. Inhibition of miR-542-5p in CB cells (thereby achieving miR-542-5p expression levels similar to SCs) promoted efficient DNA repair and activated expression of Notch reporters, HES1 and Survivin, without inducing dedifferentiation into SCs. Conclusions: Our novel framework impartially identifies therapeutically relevant miRNA candidates from transcriptomic

data sets.

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MoE publication type: A1 Journal article-refereed
Organisations: Department of Signal Processing, Research group: Computational Systems Biology, BioMediTech, Prostate cancer research center (PCRC), BioMediTech - Institute of Biosciences and Medical Technology, Hull York Medical School, Department of Urology, University of York, King's College London, University of Hull, Castle Hill Hospital, YCR Cancer Research Unit
Contributors: Rane, J. K., Ylipää, A., Adamson, R., Mann, V. M., Simms, M. S., Collins, A. T., Visakorpi, T., Nykter, M., Maitland, N. J.
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Keywords: cancer stem cell, DNA repair, epithelial hierarchy, miRNA-mRNA integration, Notch pathway, prostate cancer
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Research output: Contribution to journal › Article › Scientific › peer-review

CIP2A expression and prognostic role in patients with esophageal adenocarcinoma
CIP2A is overexpressed in many cancers, including esophageal squamous cell carcinoma. The regulation of c-MYC and CIP2A expression is characterized by a positive feedback mechanism facilitating the expression of both of them and accelerating cancer cell proliferation in gastric cancer. Increased CIP2A expression is a predictor of poor survival in some cancers. The incidence of positive CIP2A immunostaining and its association with c-MYC and its predictive value in esophageal adenocarcinoma are unknown. All esophageal adenocarcinoma patients from 1990 to 2007 with sufficient material for analysis of CIP2A and c-MYC in two university hospitals were included in the study. In addition, biopsies from Barrett's epithelium from the cancer patients and control tissue from normal esophageal mucosa adjacent to the tumor were included. CIP2A was moderately or strongly positive in 77.9 %, and c-MYC in 93.8 % of the cancer specimens. These frequencies were statistically different from the expression in normal esophageal epithelium. In addition, there was a positive correlation between CIP2A and c-MYC expression ($p = 0.018$). According to adjusted Cox regression survival analysis, CIP2A and c-MYC had no effect on survival. However, among patients with stage IVA-IVB cancer, there was a trend toward poor prognosis in CIP2Apositive patients. The expression of CIP2A and c-MYC was associated with each other, and their overexpression was found in most cases of esophageal adenocarcinoma. However, CIP2A and c-MYC had no effect on survival.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Tampere University Hospital, Helsinki University Central Hospital
Contributors: Rantanen, T., Kauttu, T., Åkerla, J., Honkanen, T., Krogerus, L., Salo, J., Paavonen, T., Oksala, N.
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Ratings:

Scopus rating (2013): CiteScore 3.2 SJR 0.902 SNIP 0.781
Original language: English
ASJC Scopus subject areas: Oncology, Cancer Research, Hematology, Medicine(all)
Keywords: C-MYC, CIP2A, Esophageal adenocarcinoma, Prognosis, Survival
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Source: Scopus
Source ID: 84880970246
Research output: Contribution to journal › Article › Scientific › peer-review

Silencing of the arp2/3 complex disturbs pancreatic cancer cell migration

Background: Actin-related protein 2/3 (ARP2/3) complex is an actin nucleator responsible for actin cytoskeleton branching which is essential for efficient cell migration. Materials and Methods: The expression of the seven ARP2/3 complex subunits was assessed in pancreatic cancer cell lines and in normal pancreatic samples by quantitative RT-PCR. siRNA-mediated silencing was used to study the contribution of each ARP2/3 complex member to pancreatic cancer cell migration. Results: ARPC3 and ARPC4 were the most highly expressed complex members, while ARPC1B and ARPC2 were expressed at low levels. Silencing of the ARP2/3 complex subunits typically resulted in reduced cell migration capacity. In particular, silencing of ARPC4 significantly reduced cell migration in all studied cell lines, with a major impact on Hs700T and HPAFII migration (50% and 68% decrease, p

General information

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Organisations: Prostate cancer research center (PCRC), Adult Stem Cells, BioMediTech, Fimlab Laboratories Ltd
Contributors: Rauhala, H. E., Teppo, S., Niemelä, S., Kallioniemi, A.
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Scopus rating (2013): CiteScore 3.2 SJR 0.816 SNIP 0.725
Original language: English
ASJC Scopus subject areas: Cancer Research, Oncology
Keywords: ARP2/3 complex, Cell migration, Pancreatic cancer
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Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

Family history in the finnish prostate cancer screening trial

Family history (FH) is one of the few known risk factors for prostate cancer (PC). There is also new evidence about mortality reduction in screening of PC with prostate-specific antigen (PSA). Therefore, we conducted a prospective study in the Finnish Prostate Cancer Screening Trial to evaluate the impact of FH on outcomes of PC screening. Of the 80,144 men enrolled, 31,866 men were randomized to the screening arm and were invited for screening with PSA test (cut-off 4 ng/ml) every 4 years. At the time of each invitation, FH of PC (FH) was assessed through a questionnaire. The analysis covered a follow-up of 12 years from randomization for all men with data on FH. Of the 23,702 (74.3%) invited men attending screening, 22,756 (96.0%) provided information of their FH. Altogether 1,723 (7.3%) men reported at least one first-degree relative diagnosed with PC and of them 235 (13.6%) were diagnosed with PC. Men with a first-degree FH had increased risk for PC (risk ratio (RR) 1.31, p <0.001) and the risk was especially elevated for interval cancer (RR 1.65, 95% CI 1.27-2.15). Risk for low-grade (Gleason 2-6) tumors was increased (RR 1.46, 95% CI 1.15-1.69), but it was decreased for Gleason 8-10 tumors (RR 0.48, 95% CI 0.25-0.95). PSA test performance (sensitivity and specificity) was slightly inferior for FH positives. No difference in PC mortality was observed in terms of FH. Our findings provide no support for selective PSA screening targeting men with FH of PC.

General information
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MoE publication type: A1 Journal article-refereed
Organisations: Prostate cancer research center (PCRC), Finnish Cancer Registry, Helsinki University Central Hospital, Tampere University Hospital, UKK Institute Finland
Contributors: Saarimäki, L., Tammela, T. L., Määttänen, L., Taari, K., Kujala, P. M., Raitanen, J., Auvinen, A.
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Scopus rating (2015): CiteScore 11 SJR 2.687 SNIP 1.555
Original language: English
ASJC Scopus subject areas: Medicine(all), Oncology, Cancer Research
Keywords: Early detection of cancer, Familial, Prostate cancer, Prostatic neoplasms, Risk factors
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Source ID: 84923124141
Research output: Contribution to journal › Article › Scientific › peer-review

Effectiveness of a 12-month exercise program on physical performance and quality of life of breast cancer survivors
Aim: The study aimed at determining whether physical exercise training improves the quality of life (QoL) and physical fitness of breast cancer survivors. Patients and Methods: A total of 573 breast cancer survivors were randomized into an exercise or a control group, 12-months after adjuvant treatments. EORTC QLQ-C30 and BR-23 questionnaires were used for evaluation of QoL, FACIT-F for fatigue and the Finnish modified version of Beck's 13-item depression scale (RBDI) for depression. Physical fitness was assessed by a 2-km walking test, and a figure-8 running test and physical activity (PA) by metabolic equivalent (MET) hours per week (MET-h/wk). Results: Figure-8 running time improved significantly among the patients of the intervention group compared with the controls (p

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Organisations: Department of Biomedical Engineering, Integrated Technologies for Tissue Engineering Research (ITTE), Helsinki University Central Hospital, UKK Institute Finland, Tampere University Hospital, Finnish Academy, Helsinki Metropolia University of Applied Sciences, Turku University Hospital, National Public Health Institute, Central Finland Central Hospital, Medcare Foundation, Pirkanmaa Cancer Society, Cancer Society of Finland, Finnish Medical Society Duodecim
Contributors: Saarto, T., Penttinen, H. M., Sievänen, H., Kellokumpu-Lehtinen, P. L., Hakamies-Blomqvist, L., Nikander, R. , Huovinen, R., Luoto, R., Kautiainen, H., Järvenpää, S., Idman, I., Utriainen, M., Vehmanen, L., Jääskeläinen, A. S., Elme, A., Ruohola, J., Palva, T., Vertio, H., Rautalahti, M., Fogelholm, M., Blomqvist, C., Luoma, M. L.
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Scopus rating (2012): CiteScore 3.3 SJR 0.788 SNIP 0.713
Original language: English
ASJC Scopus subject areas: Cancer Research, Oncology
Keywords: Breast cancer, Exercise, Oncology, Physical activity, Physical performance, Quality of life
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Source: Scopus
Source ID: 84866985052
Research output: Contribution to journal › Article › Scientific › peer-review

Podocyte apoptosis is prevented by blocking the Toll-like receptor pathway

High serum lipopolysaccharide (LPS) activity in normoalbuminuric patients with type 1 diabetes (T1D) predicts the progression of diabetic nephropathy (DN), but the mechanisms behind this remain unclear. We observed that treatment of cultured human podocytes with sera from normoalbuminuric T1D patients with high LPS activity downregulated 3-phosphoinositide-dependent kinase-1 (PDK1), an activator of the Akt cell survival pathway, and induced apoptosis. Knockdown of PDK1 in cultured human podocytes inhibited antiapoptotic Akt pathway, stimulated proapoptotic p38 MAPK pathway, and increased apoptosis demonstrating an antiapoptotic role for PDK1 in podocytes. Interestingly, PDK1 was downregulated in the glomeruli of diabetic rats and patients with type 2 diabetes before the onset of proteinuria, further suggesting that reduced expression of PDK1 associates with podocyte injury and development of DN. Treatment of podocytes in vitro and mice in vivo with LPS reduced PDK1 expression and induced apoptosis, which were prevented by inhibiting the Toll-like receptor (TLR) signaling pathway with the immunomodulatory agent GIT27. Our data show that LPS downregulates the cell survival factor PDK1 and induces podocyte apoptosis, and that blocking the TLR pathway with GIT27 may provide a non-nephrotoxic means to prevent the progression of DN.

General information

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), University of Helsinki, Department of Pathology, Laboratory Animal Centre, Helsinki University Central Hospital, Folkhälsan Institute of Genetics, Division of Nephrology, Diabetes and Obesity Research Program, University of Bristol, Baker IDI Heart and Diabetes Institute
Contributors: Saurus, P., Kuusela, S., Lehtonen, E., Hyvönen, M. E., Ristola, M., Fogarty, C. L., Tienari, J., Lassenius, M. I., Forsblom, C., Lehto, M., Saleem, M. A., Groop, P. H., Holthöfer, H., Lehtonen, S.
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ASJC Scopus subject areas: Cell Biology, Immunology, Cancer Research, Cellular and Molecular Neuroscience
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Research output: Contribution to journal › Article › Scientific › peer-review

USP22 regulates oncogenic signaling pathways to drive lethal cancer progression

Increasing evidence links deregulation of the ubiquitin-specific proteases 22 (USP22) deubitiquitylase to cancer development and progression in a select group of tumor types, but its specificity and underlying mechanisms of action are not well defined. Here we show that USP22 is a critical promoter of lethal tumor phenotypes that acts by modulating nuclear receptor and oncogenic signaling. In multiple xenograft models of human cancer, modeling of tumor-associated USP22 deregulation demonstrated that USP22 controls androgen receptor accumulation and signaling, and that it enhances expression of critical target genes coregulated by androgen receptor and MYC. USP22 not only reprogrammed androgen receptor function, but was sufficient to induce the transition to therapeutic resistance. Notably, in vivo depletion experiments revealed that USP22 is critical to maintain phenotypes associated with end-stage disease. This was a significant finding given clinical evidence that USP22 is highly deregulated in tumors, which have achieved therapeutic resistance. Taken together, our findings define USP22 as a critical effector of tumor progression, which drives lethal phenotypes, rationalizing this enzyme as an appealing therapeutic target to treat advanced disease.

General information

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Organisations: Prostate cancer research center (PCRC), Thomas Jefferson University, Johns Hopkins University, School of Management (JKK)
Contributors: Schrecengost, R. S., Dean, J. L., Goodwin, J. F., Schiewer, M. J., Urban, M. W., Stanek, T. J., Sussman, R. T., Hicks, J. L., Birbe, R. C., Draganova-Tacheva, R. A., Visakorpi, T., DeMarzo, A. M., McMahon, S. B., Knudsen, K. E.

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Source: Scopus
Source ID: 84892694492
Research output: Contribution to journal › Article › Scientific › peer-review

European code against cancer 4th edition: 12 ways to reduce your cancer risk
This overview describes the principles of the 4th edition of the European Code against Cancer and provides an introduction to the 12 recommendations to reduce cancer risk. Among the 504.6 million inhabitants of the member states of the European Union (EU28), there are annually 2.64 million new cancer cases and 1.28 million deaths from cancer. It is estimated that this cancer burden could be reduced by up to one half if scientific knowledge on causes of cancer could be translated into successful prevention. The Code is a preventive tool aimed to reduce the cancer burden by informing people how to avoid or reduce carcinogenic exposures, adopt behaviours to reduce the cancer risk, or to participate in organised intervention programmes. The Code should also form a base to guide national health policies in cancer prevention. The 12 recommendations are: not smoking or using other tobacco products; avoiding second-hand smoke; being a healthy body weight; encouraging physical activity; having a healthy diet; limiting alcohol consumption, with not drinking alcohol being better for cancer prevention; avoiding too much exposure to ultraviolet radiation; avoiding cancer-causing agents at the workplace; reducing exposure to high levels of radon; encouraging breastfeeding; limiting the use of hormone replacement therapy; participating in organised vaccination programmes against hepatitis B for newborns and human papillomavirus for girls; and participating in organised screening programmes for bowel cancer, breast cancer, and cervical cancer.

General information
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Organisations: Prostate cancer research center (PCRC), International Agency for Research on Cancer, University Hospital 'Citta della Salute e della Scienza', University College London, World Cancer Research Fund International, Istituto Superiore di Sanita, World Health Organization, Oncology Institute of Southern Switzerland, World Health Organization Regional Office for Europe, Institut Gustave Roussy, Universitat Politecnica de Valencia, Spain, Oncology Institute 'Prof. Dr I. Chiricuta', Danish Cancer Society Research Center, Public Health England, Institute of Oncology, National Public Health Institute, Netherlands Cancer Institute, German Cancer Research Center, Institute of Oncology, Warsaw
Contributors: Schüz, J., Espina, C., Villain, P., Herrero, R., Leon, M. E., Minozzi, S., Romieu, I., Segnan, N., Wardle, J., Wiseman, M., Belardelli, F., Bettcher, D., Cavalli, F., Galea, G., Lenoir, G., Martin-Moreno, J. M., Nicula, F. A., Olsen, J. H. , Patnick, J., Primic-Zakelj, M., Puska, P., Van Leeuwen, F. E., Wiestler, O., Zatonski, W., Guha, N., Kralikova, E., McNeill, A., Peruga, A., Anderson, A., Berrino, F., Boutron-Ruault, M. C., Cecchini, M., Key, T. J., Leitzmann, M., Norat, T. , Powers, H. J., Scoccianti, C., Auvinen, A., de Vries, E., Erdmann, F., Greinert, R., Harrison, J., Kesminiene, A., McColl, N., Friis, S., Kogevinas, M., Saracci, R., Straif, K., Vainio, H., Almonte, M., Anttila, A., De Vuyst, H., Dillner, J., Franceschi, S., Gonzalez, P., Hall, A., Park, J. Y., Armaroli, P., Atkin, W., Dean, P. B., de Koning, H., Dillner, L., Kuipers, E., Lansdorp-Vogelaar, I., Paci, E., Regula, J., Suonio, E., Törnberg, S., Wood, L. F., Gaudin, N., Frie, K. G., Terrasse, V. , Winstanley, K., Bellisario, C., Biagioli, E., Cinquini, M., Gianola, S., Lorenzo, M. G., von Karsa, L., Lignini, T.
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Keywords: Cancer prevention, Cancer risk factors, Cancer screening, Europe
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Research output: Contribution to journal › Article › Scientific › peer-review

An international prospective cohort study of mobile phone users and health (Cosmos): Design considerations and enrolment

Background: There is continuing public and scientific interest in the possibility that exposure to radiofrequency (RF) electromagnetic fields (EMF) from mobile telephones or other wireless devices and applications might increase the risk of certain cancers or other diseases. The interest is amplified by the rapid world-wide penetration of such technologies. The evidence from epidemiological studies published to date have not been consistent and, in particular, further studies are required to identify whether longer term (well beyond 10 years) RF exposure might pose some health risk. Methods: The "Cosmos" study described here is a large prospective cohort study of mobile telephone users (ongoing recruitment of 250,000 men and women aged 18+ years in five European countries - Denmark, Finland, Sweden, The Netherlands, UK) who will be followed up for 25+ years. Information on mobile telephone use is collected prospectively through questionnaires and objective traffic data from network operators. Associations with disease risks will be studied by linking cohort members to existing disease registries, while changes in symptoms such as headache and sleep quality and of general well-being are assessed by baseline and follow-up questionnaires. Conclusions: A prospective cohort study conducted with appropriate diligence and a sufficient sample size, overcomes many of the shortcomings of previous studies. Its major advantages are exposure assessment prior to the diagnosis of disease, the prospective collection of objective exposure information, long-term follow-up of multiple health outcomes, and the flexibility to investigate future changes in technologies or new research questions.

General information

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Organisations: Prostate cancer research center (PCRC), Institute of Cancer Epidemiology - Denmark, Imperial College, London, 24.8.2012, STUK - Radiation and Nuclear Safety Authority, Utrecht University, Karolinska Institutet
Contributors: Schüz, J., Elliott, P., Auvinen, A., Kromhout, H., Poulsen, A. H., Johansen, C., Olsen, J. H., Hillert, L., Feychting, M., Fremling, K., Toledano, M., Heinävaara, S., Slottje, P., Vermeulen, R., Ahlbom, A.
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Scopus rating (2011): CiteScore 2.5 SJR 0.78 SNIP 0.902
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ASJC Scopus subject areas: Epidemiology, Oncology, Cancer Research
Keywords: Brain neoplasms, Cellular phone, Cohort studies, Electromagnetic fields, Epidemiology, Radiation non-ionising , Risk assessment
DOIs:

10.1016/j.canep.2010.08.001
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Research output: Contribution to journal › Article › Scientific › peer-review

A DNA methylation microarray-based study identifies ERG as a gene commonly methylated in prostate cancer

DNA methylation of promoter regions is a common event in prostate cancer, one of the most common cancers in men worldwide. Because prior reports demonstrating that DNA methylation is important in prostate cancer studied a limited

number of genes, we systematically quantified the DNA methylation status of 1,505 CpG dinucleotides for 807 genes in 78 paraffin-embedded prostate cancer samples and three normal prostate samples. The ERG gene, commonly repressed in prostate cells in the absence of an oncogenic fusion to the TMPRSS2 gene, was one of the most commonly methylated genes, occurring in 74% of prostate cancer specimens. In an independent group of patient samples, we confirmed that ERG DNA methylation was common, occurring in 57% of specimens, and cancer-specific. The ERG promoter is marked by repressive chromatin marks mediated by polycomb proteins in both normal prostate cells and prostate cancer cells, which may explain ERG's predisposition to DNA methylation and the fact that tumors with ERG DNA methylation were more methylated, in general. These results demonstrate that bead arrays offer a high-throughput method to discover novel genes with promoter DNA methylation such as ERG, whose measurement may improve our ability to more accurately detect prostate cancer.

General information
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Organisations: Prostate cancer research center (PCRC), Division of Hematology and Oncology, Oregon Health and Science University, University of Washington Medical Center, Department of Pathology, Johns Hopkins University, Oregon Clinic
Contributors: Schwartzman, J., Mongoue-Tchokote, S., Gibbs, A., Gao, L., Corless, C. L., Jin, J., Zarour, L., Higano, C., True, L. D., Vessella, R. L., Wilmot, B., Bottomly, D., McWeeney, S. K., Bova, S. G., Partin, A. W., Mori, M., Alumkal, J. J.
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Peer-reviewed: Yes

Publication information
Journal: EPIGENETICS
Volume: 6
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ISSN (Print): 1559-2294
Ratings:

Scopus rating (2011): CiteScore 5.1 SJR 2.211 SNIP 0.781
Original language: English
ASJC Scopus subject areas: Molecular Biology, Cancer Research
Keywords: Biomarker, DNA methylation, ERG, Polycomb, Prostate cancer
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Source: Scopus
Source ID: 80053458910
Research output: Contribution to journal › Article › Scientific › peer-review

The concurrent use of aromatase inhibitors and radiotherapy induces echocardiographic changes in patients with breast cancer

Aim: Adjuvant radiotherapy (RT) for left-sided breast cancer has a negative impact on cardiac health. The concurrent use of aromatase inhibitors (AIs) during RT was found to increase the anticancer efficacy of radiation in preclinical models. We evaluated whether the acute effects of RT on cardiac functions are augmented by the concurrent use of AIs. Patients and Methods: Sixty patients with early-stage left-sided breast cancer underwent a 2D echocardiography, electrocardiogram and cardiac biomarker measurements before and after adjuvant breast RT. Data were analyzed in two groups according to AI use. Results: We observed a significant (p

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE)
Contributors: Skyttä, T., Tuohinen, S., Virtanen, V., Raatikainen, P., Kellokumpu-Lehtinen, P. L.
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Original language: English
ASJC Scopus subject areas: Cancer Research, Oncology, Medicine(all)
Keywords: Aromatase inhinitors, Breast cancer, Cardiotoxicity, Radiotherapy
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Research output: Contribution to journal › Article › Scientific › peer-review

Sarcopenia during androgen-deprivation therapy for prostate cancer

Purpose: To characterize changes in lean body mass (LBM) in men with prostate cancer receiving androgen-deprivation therapy (ADT). Patients and Methods: We prospectively evaluated LBM in a prespecified substudy of a randomized controlled trial of denosumab to prevent fractures in men receiving ADT for nonmetastatic prostate cancer. LBM was measured by total-body dual-energy x-ray absorptiometry at study baseline and at 12, 24, and 36 months. The analyses included 252 patients (132, denosumab; 120, placebo) with a baseline and at least one on-study LBM assessment. Patients were stratified by age (<70 v ≥ 70 years) and by ADT duration (≤ 6 v > 6 months). Results: Median ADT duration was 20.4 months at study baseline. Mean LBM decreased significantly from baseline, by 1.0% at month 12 (95% CI, 0.4% to 1.5%; P <.001; n = 248), by 2.1% at month 24 (95% CI, 1.5% to 2.7%; P <.001; n = 205), and by 2.4% at month 36 (95% CI, 1.6% to 3.2%; P <.001; n = 168). Men age ≥ 70 years (n = 127) had significantly greater changes in LBM at all measured time points than younger men. At 36 months, LBM decreased by 2.8% in men age ≥ 70 years and by 0.9% in younger men (P = .035). Men with ≤ 6 months of ADT at study entry (n = 36) had a greater rate of decrease in LBM compared with men who had received more than 6 months of ADT at study entry (3.7% v 2.0%; P = .0645). Conclusion: In men receiving ADT, LBM decreased significantly after 12, 24, and 36 months.

General information

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Organisations: Prostate cancer research center (PCRC), Massachusetts General Hospital Cancer Center, Centre Hospitalier de l'Université de Montréal, Urology Associates Urologic Medical Research, Urologic Associates, Tampere University Hospital, Amgen Incorporated, Massachusetts General Hospital
Contributors: Smith, M. R., Saad, F., Egerdie, B., Sieber, P. R., Tammela, T. L. J., Ke, C., Leder, B. Z., Goessl, C.
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Human breast cancer cells educate macrophages toward the M2 activation status

Introduction: The immune system plays a major role in cancer progression. In solid tumors, 5-40 % of the tumor mass consists of tumor-associated macrophages (TAMs) and there is usually a correlation between the number of TAMs and poor prognosis, depending on the tumor type. TAMs usually resemble M2 macrophages. Unlike M1-macrophages which have pro-inflammatory and anti-cancer functions, M2-macrophages are immunosuppressive, contribute to the matrix-remodeling, and hence favor tumor growth. The role of TAMs is not fully understood in breast cancer progression. Methods: Macrophage infiltration (CD68) and activation status (HLA-DRIIaα, CD163) were evaluated in a large cohort of human primary breast tumors (562 tissue microarray samples), by immunohistochemistry and scored by automated image analysis algorithms. Survival between groups was compared using the Kaplan-Meier life-table method and a Cox

multivariate proportional hazards model. Macrophage education by breast cancer cells was assessed by ex vivo differentiation of peripheral blood mononuclear cells (PBMCs) in the presence or absence of breast cancer cell conditioned media (MDA-MB231, MCF-7 or T47D cell lines) and M1 or M2 inducing cytokines (respectively IFN-γ, IL-4 and IL-10). Obtained macrophages were analyzed by flow cytometry (CD14, CD16, CD64, CD86, CD200R and CD163), ELISA (IL-6, IL-8, IL-10, monocyte colony stimulating factor M-CSF) and zymography (matrix metalloproteinase 9, MMP-9). Results: Clinically, we found that high numbers of $CD163^{+}$ M2-macrophages were strongly associated with fast proliferation, poor differentiation, estrogen receptor negativity and histological ductal type (p

General information
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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), Ita-Suomen yliopisto, CHU de Nantes, Turun Yliopisto/Turun Biomateriaalikeskus, Turku Centre for Biotechnology, University of Tampere, Medical School, University of Helsinki, Haartman Institute, Helsinki University Central Hospital
Contributors: Sousa, S., Brion, R., Lintunen, M., Kronqvist, P., Sandholm, J., Mönkkönen, J., Kellokumpu-Lehtinen, P. L., Lauttia, S., Tynninen, O., Joensuu, H., Heymann, D., Määttä, J. A.
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Survival benefit of early androgen receptor inhibitor therapy in locally advanced prostate cancer: Long-term follow-up of the SPCG-6 study
Background The optimal timing of endocrine therapy in non-metastatic prostate cancer (PCa) is still an issue of debate. Methods A randomised, double-blind, parallel-group trial comparing bicalutamide 150 mg once daily with placebo in addition to standard care in patients with hormone-naïve, non-metastatic PCa. Kaplan-Meier analysis was used to estimate overall survival (OS) and multivariate Cox proportional hazard model was performed to analyse time-to-event (death). Findings A total of 1218 patients were included into the Scandinavian Prostate Cancer Group (SPCG)-6 study of which 607 were randomised to receive bicalutamide in addition to their standard care and 611 to receive placebo. Median follow-up was 14.6 years. Overall, 866 (71.1%) patients died, 428 (70.5%) in the bicalutamide arm and 438 (71.7%) in the placebo arm, p = 0.87. Bicalutamide significantly improved OS in patient with locally advanced disease (hazard ratios (HR) = 0.77 (95% confidence interval (CI): 0.63-0.94, p = 0.01), regardless of baseline prostate-specific antigen (PSA), with a survival benefit which was apparent throughout the study period. In contrast, survival favoured randomisation to the placebo arm in patients with localised disease (HR = 1.19 (95% CI: 1.00-1.43), p = 0.056). However, a survival gain from bicalutamide therapy was present in patients with localised disease and a baseline PSA greater than 28 ng/mL at randomisation. In multivariate Cox proportional hazard model, only including patients managed on watchful waiting as their standard of care (n = 991) OS depended on age, World Health Organisation (WHO) grade, baseline PSA, clinical stage and randomised treatment. Interpretation Throughout the 14.6 year follow-up period the addition of early bicalutamide to standard of care resulted in a significant OS benefit in patients with locally advanced PCa. In contrast, patients with localised PCa and low PSA derived no survival benefit from early bicalutamide. The optimal timing for initiating bicalutamide in non-metastatic PCa patients is dependent on disease stage and baseline PSA.

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Organisations: Prostate cancer research center (PCRC), Kobenhavns Universitet, Örebro University, Norwegian Univ. of Sci. and Technol.
Contributors: Thomsen, F. B., Brasso, K., Christensen, I. J., Johansson, J. E., Angelsen, A., Tammela, T. L. J., Iversen, P.
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A Novel MMP12 Locus Is Associated with Large Artery Atherosclerotic Stroke Using a Genome-Wide Age-at-Onset Informed Approach

Genome-wide association studies (GWAS) have begun to identify the common genetic component to ischaemic stroke (IS). However, IS has considerable phenotypic heterogeneity. Where clinical covariates explain a large fraction of disease risk, covariate informed designs can increase power to detect associations. As prevalence rates in IS are markedly affected by age, and younger onset cases may have higher genetic predisposition, we investigated whether an age-at-onset informed approach could detect novel associations with IS and its subtypes; cardioembolic (CE), large artery atherosclerosis (LAA) and small vessel disease (SVD) in 6,778 cases of European ancestry and 12,095 ancestry-matched controls. Regression analysis to identify SNP associations was performed on posterior liabilities after conditioning on age-at-onset and affection status. We sought further evidence of an association with LAA in 1,881 cases and 50,817 controls, and examined mRNA expression levels of the nearby genes in atherosclerotic carotid artery plaques. Secondly, we performed permutation analyses to evaluate the extent to which age-at-onset informed analysis improves significance for novel loci. We identified a novel association with an MMP12 locus in LAA (rs660599; $p = 2.5\times10^{-7}$), with independent replication in a second population ($p = 0.0048$, OR(95% CI) = 1.18(1.05-1.32); meta-analysis $p = 2.6\times10^{-8}$). The nearby gene, MMP12, was significantly overexpressed in carotid plaques compared to atherosclerosis-free control arteries ($p = 1.2\times10^{-15}$; fold change = 335.6). Permutation analyses demonstrated improved significance for associations when accounting for age-at-onset in all four stroke phenotypes (p

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Organisations: Integrated Technologies for Tissue Engineering Research (ITTE), St George's University of London, Hunter Medical Research Institute, Australia, Broad Institute, National Institute on Aging, Visiting Graduate Student in Department of Urban Design and Planning, University of Washington, Seattle, USA 1.1.2012-15.6.2012 (12.9.2011 alkaen), University of Pennsylvania, Veterans Affairs Maryland Health Care System, University Medical Center Utrecht, Institute for Stroke and Dementia Research, Klinikum der Universität München, Ludwig-Maximilians-Universität, University of Edinburgh, University of Cambridge, Tampere University Hospital, University Hospital Gasthuisberg, Skåne University Hospital, Uniwersytet Jagiellonski w Krakowie, University of Newcastle, Australia, University of Glasgow, Imperial College, London, 24.8.2012, Istituto Neurologico Carlo Besta, University of Oxford, Brigham and Women's Hospital, Center for Non-Communicable Diseases, University of Maryland School of Medicine, Mayo Clinic in Jacksonville, Florida, Ludwig Maximilian University, King's College London
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Research output: Contribution to journal › Article › Scientific › peer-review

Early effects of adjuvant breast cancer radiotherapy on right ventricular systolic and diastolic function

Aim: Reduced right ventricular (RV) systolic function correlates with poor prognosis in several heart diseases. The aim of this prospective single-Center study was to investigate whether conformal three-dimensional (3D) breast cancer radiotherapy impairs RV function. Patients and Methods: Forty-nine patients with early-stage left-sided breast cancer underwent comprehensive two-dimensional (2D) echocardiography before and after radiotherapy. RV function was evaluated with tricuspid annular plane systolic excursion (TAPSE), pulsed tissue Doppler peak velocity at the lateral RV wall (S') and RV and venous flow analysis. Results: Radiotherapy reduced TAPSE from 24.5±4.0 mm to 22.4±3.9 mm (p

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Contributors: Tuohinen, S. S., Skyttä, T., Virtanen, V., Luukkaala, T., Kellokumpu-Lehtinen, P. L., Raatikainen, P.
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Research output: Contribution to journal › Article › Scientific › peer-review

Intraprostatic inflammation is positively associated with serum PSA in men with PSA <4 ngml^{-1}, normal DRE and negative for prostate cancer

Biopsies performed for elevated serum PSA often show inflammatory infiltrates. However, the influence of intraprostatic inflammation on serum PSA in men without biopsy indication and negative for prostate cancer has not been described in detail.Methods:We studied 224 men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) who underwent end-of-study biopsy per trial protocol, had PSA -1, normal digital rectal examination and a biopsy negative for cancer. We analyzed data from hematoxylin and eosin-stained slides containing a mean of three biopsy cores. Inflammation measures included the extent (percentage of tissue area with inflammation) and intensity (product of scores for extent and grade) of total, acute and chronic inflammation in the entire tissue area examined, and by tissue compartment. We calculated median measures of inflammation by prebiopsy serum PSA tertile (>0 to ≤0.8, >0.8 to ≤1.5 and >1.5 to -1). We estimated the association between percentage of tissue area with inflammation and natural logarithm of PSA using linear regression adjusting for age at biopsy.Results:Median percentage of tissue area with inflammation increased from 2 to 5 to 9.5% across PSA tertiles (P-trend -1 (P=0.0002). Median extent and intensity scores increased across PSA tertiles in luminal and intraepithelial compartments for acute inflammation and in stromal and intraepithelial compartments for chronic inflammation (all P-trend ≤0.05).Conclusions:In men without clinical suspicion of prostate cancer, greater overall inflammation, luminal and intraepithelial acute inflammation and stromal and intraepithelial chronic inflammation were

associated with higher serum PSA.

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Contributors: Umbehr, M. H., Gurel, B., Murtola, T. J., Sutcliffe, S., Peskoe, S. B., Tangen, C. M., Goodman, P. J., Thompson, I. M., Lippman, S. M., Lucia, M. S., Parnes, H. L., Drake, C. G., Nelson, W. G., De Marzo, A. M., Platz, E. A.
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Source: Scopus
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Research output: Contribution to journal › Article › Scientific › peer-review

Prostate cancer risk and nonsteroidal antiinflammatory drug use in the Finnish prostate cancer screening trial.

The association between nonsteroidal antiinflammatory drugs (NSAIDs) and prostate cancer risk remains controversial. We examined the risk among NSAID users in 78 615 men in the Finnish Prostate Cancer Screening Trial. We obtained information on NSAID prescription usage from Finnish nationwide prescription database and on over-the-counter use by a questionnaire. Prostate cancer cases were identified from the Finnish Cancer Registry. Prostate cancer risk was elevated among current NSAID prescription users irrespective of screening (hazard ratio (HR)=1.45, confidence interval (95% CI)=1.33-1.59 and HR=1.71, 95% CI=1.58-1.86 in the screening and control arm, respectively), but not for previous use of NSAIDs. The risk increase was similar among coxib and acetaminophen current users, and stronger for metastatic prostate cancer (HR=2.41, 95% CI=1.59-3.67 and HR=3.44, 95% CI=2.60-4.55 in the screening and control arm, respectively). Previous use of NSAIDs, aspirin use and over-the-counter NSAID usage were not associated with prostate cancer. Differing association for current and previous use suggests that the risk increase is unlikely to be directly caused by the medication, but may be due to the conditions indicating NSAID prescription usage, such as symptoms of undiagnosed prostate cancer. To reduce inconsistency between the study outcomes, future epidemiological studies on NSAID use and prostate cancer risk should assess the indications for NSAID usage.

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Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Finnish Cancer Registry, Helsinki University Central Hospital
Contributors: Veitonmäki, T., Murtola, T. J., Määttänen, L., Taari, K., Stenman, U. H., Tammela, T. L., Auvinen, A.
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Source ID: 84909992770
Research output: Contribution to journal › Article › Scientific › peer-review

Use of aspirin, but not other non-steroidal anti-inflammatory drugs is associated with decreased prostate cancer risk at the population level

The cyclooxygenase 2 (COX-2) enzyme overexpression in prostate cancer has led to the hypothesis that COX-2 inhibition may reduce prostate cancer growth. Some previous studies have linked the usage of COX-2 inhibiting non-steroidal anti-inflammatory drugs (NSAIDs) with a decreased prostate cancer risk. We estimated the association between cumulative COX-2 inhibition by NSAID usage and prostate cancer risk at population level. All new prostate cancer cases in Finland during 1995-2002 and matched controls (24,657 case-control pairs) were identified from national registries. Detailed information on medication purchases was obtained from a national prescription database. A total cumulative COX-2 inhibition value was calculated based on total cumulative mg amount of each NSAID drug and the drug-specific COX-1/COX-2 inhibition ratio. Prostate cancer risk was analysed with propensity score-matched conditional logistic regression model. In total, 53.8% of the cases and 46.5% of the controls had any prescription-use of NSAIDs, while 8.1% and 7.9%, respectively, had used aspirin. Compared to the non-users, any NSAID use was associated with an elevated overall prostate cancer risk (46.4% versus 53.6%, respectively; odds ratio [OR] 1.3, 95% confidence interval [CI] 1.3, 1.4) and risk of advanced cancer (11.8% versus 14.1%; OR 1.6, 95% CI 1.5, 1.8). The risk remained elevated despite the amount of cumulative COX-2 inhibition. In a separate analysis, the risk increase was similar for each NSAID with the exception of aspirin, which was associated with a decreased overall prostate cancer risk (OR 0.90, 95% CI 0.84, 0.96) in a dose-dependent fashion. NSAID use is associated with an increased prostate cancer risk at the population level regardless of the COX-2 inhibition. This may be explained by systematic differences between prescription NSAID users and non-users. In contrast, aspirin use is associated with a decreased overall prostate cancer risk. Further studies on aspirin and prostate cancer will be needed.

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Organisations: Prostate cancer research center (PCRC), Tampere University Hospital, Central Finland Central Hospital
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Research output: Contribution to journal › Article › Scientific › peer-review

Altered polyamine profiles in colorectal cancer

Background: The declining mortality rate of patients with colorectal cancer (CRC) can be explained, at least partially, with early diagnosis. Simple diagnostic methods are needed to achieve a maximal patient participation rate in screening. Materials and Methods: Liquid chromatography electrospray tandem mass spectrometry (LC-MS/MS) was used to

determine urinary polyamine (PA) profiles. In a prospective setting, 116 patients were included in the study: 57 with CRC, 13 with inflammatory bowel disease (IBD), 12 with adenoma, and 34 controls. Results: N1,N12-diacetylspermine (DiAcSPM) level was significantly higher in patients with CRC than controls (sensitivity=78.0%, specificity=70.6%; p=0.00049). The level of diacetylated cadaverine (p=0.0068) was lower and that of diacetylated putrescine (p=0.0078) was higher in patients with CRC than in those with IBD. Cadaverine (p=0.00010) and spermine (p=0.042) levels were lower and that of DiAcSPM (p=0.018) higher in patients with CRC than in those with adenoma. Conclusion: The simultaneous determination of urinary PAs by means of LC-MS/MS can be used to discriminate CRC from controls and patients with benign colorectal diseases.

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Organisations: Faculty of Biomedical Sciences and Engineering, Ita-Suomen yliopisto, University Central Hospital Kuopio, Hatanpää Hospital, Fimlab Laboratories Ltd, Tampere University Hospital, Central Hospital of Seinäjoki
Contributors: Venäläinen, M. K., Roine, A. N., Häkkinen, M. R., Vepsäläinen, J. J., Kumpulainen, P. S., Kiviniemi, M. S., Lehtimäki, T., Oksala, N. K., Rantanen, T. K.
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Microarray analysis of differentially expressed genes in ovarian and fallopian tube epithelium from risk-reducing salpingo-oophorectomies
Mutations in the BRCA1 and BRCA2 genes confer an increased lifetime risk for breast and ovarian cancer. Ovarian cancer risk can be decreased by risk-reducing salpingo-oophorectomy (RRSO). Studies on RRSO material have altered the paradigm of serous ovarian cancer pathogenesis. The purpose of this study was to identify candidate genes possibly involved in the pathogenesis of serous ovarian cancer by carrying out a microarray analysis of differentially expressed genes in BRCA1/2- mutation positive ovarian and fallopian tube epithelium derived from RRSO surgery. Freshly frozen ovarian and fallopian tube samples from nine BRCA1/2 mutation carriers scheduled for RRSO were prospectively collected together with five mutation-negative control patients undergoing salpingo-oophorectomy for benign indications. Microarray analysis of genome-wide gene expression was performed on ovarian and fallopian tube samples from the BRCA1/2 and control patients. The validation of microarray data was performed by quantitative real-time polymerase chain reaction (qRT-PCR) in selected cases of RRSO samples and also in high grade serous carcinoma samples collected from patients with a BRCA phenotype. From 22,733 genes, 454 transcripts were identified that were differentially expressed in BRCA1/2 mutation carriers when compared with controls, pooling all ovarian and fallopian tube samples together. Of these, 299 genes were statistically significantly downregulated and 155 genes upregulated. Differentially expressed genes in BRCA1/2 samples reported here might be involved in serous ovarian carcinogenesis and provide interesting targets for further studies.

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Organisations: Department of Signal Processing, Research group: Computational Systems Biology, BioMediTech, Multi-scaled biodata analysis and modelling (MultiBAM), Tampere University Hospital, University of Tampere
Contributors: Veskimäe, K., Staff, S., Tabaro, F., Nykter, M., Isola, J., Mäenpää, J.
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Circulating levels of VEGFR-1 and VEGFR-2 in patients with metastatic melanoma treated with chemoimmunotherapy alone or combined with bevacizumab

There are no identified biomarkers that could predict response to antiangiogenic or traditional chemoimmunotherapy in metastatic melanoma. We hypothesized that soluble angiogenic factor receptors might help us to identify patients responsive to treatment. A series of 48 patients with stage IV melanoma participating in two phase II clinical trials were included. The trials included treatment with carboplatin, vinorelbine, and subcutaneous interleukin-2 (n=22) or treatment with bevacizumab, dacarbazine, and low-dose interferon-α2a (n=26).Serum samples were prospectively collected and soluble vascular endothelial growth factor receptor 1 (s-VEGFR-1) and 2 (s-VEGFR-2) were measured before starting the trial treatment and during response evaluation.There was a trend toward longer overall survival among patients with higher-than-median serum VEGFR-1 levels (21.3 months) compared with 12.3 months in patients with low pretreatment s-VEGFR-1 levels (P=0.146). Pretreatment s-VEGFR-2 levels did not correlate to survival. Serum VEGFR-2 levels decreased during therapy in 44% of the patients and increased in 56% of the patients. VEGFR-2 increased in 78% (14 of 18) of the patients who progressed during therapy (P=0.017). VEGFR-2 decrease was associated with clinical benefit in 65% of the patients (11 of 17) and with progression in only four patients (P=0.016).High pretreatment levels of s-VEGFR-1 are associated with improved prognosis among patients with metastatic melanoma independently on therapy, whereas increased VEGFR-2 levels during therapy are associated with disease progression. These markers might be useful in selecting patients responsive to antiangiogenic therapy.

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Contributors: Vihinen, P. P., Ramadan, S., Vuoristo, M. S., Hernberg, M., Tyynelä-Korhonen, K., Skyttä, T., Koskivuo, I., Kellokumpu-Lehtinen, P. L., Syrjänen, K., Pyrhönen, S.
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Research output: Contribution to journal › Article › Scientific › peer-review

VEGFR3 and CD31 as prognostic factors in renal cell cancer

Aim: To evaluate the expression levels of vascular endothelial growth factor receptor-3 (VEGFR3) and CD31 and assess their associations with grade, stage and survival in patients with renal cell cancer (RCC). Patients and Methods: Our study included 224 consecutive patients who received treatment during the years 1985-1995 in Tampere Finland but had not been treated with modern antiangiogenesis drugs. All tumor samples were re-classified and investigated using immunohistological techniques. Data were collected from patient records and the Finnish Cancer Registry. Results: In total, 54.2% and 98.2% of the tumor samples tested positive for VEGFR3 and CD31 expression, respectively. CD31 expression levels were classified into two groups according to the median level revealing that its high expression was nearly significantly associated with low tumor stage (p=0.069). In an age- and gender-adjusted analysis, low expression of CD31 associated with poorer survival. Grade 3 and grade 4 tumors had significantly higher mortality rates compared to those of grades 1-2 (hazard ratio (HR)=4.91; 95% confidence interval (CI)=1.12-20.4; p=0.029 for grade 3 and HR=9.31; 95% CI=2.23-38.8; p=0.002 for grade 4). In addition, stage 2, 3 and 4 tumors revealed that they possessed significantly higher mortality hazard ratios compared to those of stage 1 tumors (HR=2.62; 95% CI=1.27-5.41; p=0.009 for stage 2, HR=4.37;95% CI=2.29-8.3; p

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Claudins as prognostic factors for renal cell cancer

Background: Claudins are tight junction proteins and their expression is often different in normal and corresponding tumor cells. In the present study, we determined how the expression of claudins 1-5 and 7 correlated to survival, grade and stage of patients with renal cell cancer (RCC). Patients and Methods: Primary tumor samples were collected retrospectively from 229 RCC patients. Claudins were detected by immunohistochemistry using commercial monoclonal antibodies against claudins 1-5 and 7. Median survival time was 6.5 years confidence interval (CI) (4.5-8.5, n=224). Kaplan-Meier survival estimated method was used in survival analyses. Results: Positive expression was detected in 62%, 67%, 45%, 55%, 7% and 35% of cases for claudins 1, 2, 3, 4, 5 and 7, respectively. High expression of claudin 2 was observed in 20% of cases while high expression of other claudins was less frequent. Claudins were compared to classical prognostic factors. On cross-tabulation, claudin 1 (p

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Depletion of nuclear import protein karyopherin alpha 7 (KPNA7) induces mitotic defects and deformation of nuclei in cancer cells

Background: Nucleocytoplasmic transport is a tightly regulated process carried out by specific transport machinery, the defects of which may lead to a number of diseases including cancer. Karyopherin alpha 7 (KPNA7), the newest member of the karyopherin alpha nuclear importer family, is expressed at a high level during embryogenesis, reduced to very low or absent levels in most adult tissues but re-expressed in cancer cells. Methods: We used siRNA-based knock-down of KPNA7 in cancer cell lines, followed by functional assays (proliferation and cell cycle) and immunofluorescent stainings to determine the role of KPNA7 in regulation of cancer cell growth, proper mitosis and nuclear morphology. Results: In the present study, we show that the silencing of KPNA7 results in a dramatic reduction in pancreatic and breast cancer cell growth, irrespective of the endogenous KPNA7 expression level. This growth inhibition is accompanied by a decrease in the fraction of S-phase cells as well as aberrant number of centrosomes and severe distortion of the mitotic spindles. In addition, KPNA7 depletion leads to reorganization of lamin A/C and B1, the main nuclear lamina proteins, and drastic alterations in nuclear morphology with lobulated and elongated nuclei. Conclusions: Taken together, our data provide new important evidence on the contribution of KPNA7 to the regulation of cancer cell growth and the maintenance of nuclear envelope environment, and thus deepens our understanding on the impact of nuclear transfer proteins in cancer pathogenesis.

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The Association Between Liver and Tumor [^{18}F]FDG Uptake in Patients with Diffuse Large B Cell Lymphoma During Chemotherapy

Purpose: The aim of this study was to explore the association between liver, mediastinum and tumor 2-deoxy-2-[^{18}F]fluoro-d-glucose ([^{18}F]FDG) uptake during chemotherapy in diffuse large B cell lymphoma (DLBCL). Procedures: Nineteen patients with proven DLBCL underwent positron emission tomography (PET)/X-ray computed tomography scan at baseline, 1 week and 2 cycles after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy, and again after chemotherapy completion. The mean and maximal standardized uptake value (SUVmean and SUVmax) of the liver and mediastinum were measured and correlated with the tumor SUVmax, SUVsum, whole-body metabolic tumor volume (MTVwb), and total lesion glycolysis (TLG). Results: At baseline, both the liver and mediastinum SUVmean and SUVmax correlated inversely with the tumor MTVwb or TLG ($p < 0.01$ or 0.001). The liver SUVmean and SUVmax increased significantly after 1 week of R-CHOP therapy and remained at the high level until chemotherapy completion. The mediastinum SUVmean and SUVmax remained stable during chemotherapy. The tumor SUVmax, SUVsum, MTVwb, and TLG decreased significantly after 1 week of R-CHOP therapy. The change of the liver SUVmean correlated inversely with the change of tumor MTVwb and TLG after 1 week of chemotherapy ($p < 0.05$, respectively). The intersubject variability of liver and mediastinum [^{18}F]FDG uptake ranged from 11 to 26 %. Conclusions: The liver [^{18}F]FDG uptake increased significantly after R-CHOP therapy. One of the possible reasons is the distribution of a greater fraction of the tracer to healthy tissues rather than tumor after effective chemotherapy. The variability of the liver [^{18}F]FDG uptake during chemotherapy might affect the visual analysis of the interim PET scan and this needs to be confirmed in future studies with a large patient cohort. In addition, the intersubject variability of the liver and mediastinum [^{18}F]FDG uptake should be considered.

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Number of screens for overdetection as an indicator of absolute risk of overdiagnosis in prostate cancer screening

As with wide-spread use of prostate cancer (Pca) screening with prostate-specific antigen testing, overdetection has increasingly gained attention. The authors aimed to estimate absolute risk of overdetection (RO) in Pca screening with various interscreening intervals and ages at start of screening. We estimated age-specific preclinical incidence rates (per 100,000 person-years) for progressive cancer (from 128 for age group 55-58 years to 774 for age group 67-71 years) and nonprogressive cancer (from 40 for age group 55-58 years to 66 for age group 67-71 years), the mean sojourn time (7.72 years) and the sensitivity (42.8% at first screen and 59.8% at the second screen) by using a multistep epidemiological model with data from the Finnish randomized controlled trial. The overall number of screens for overdetection (NSO) was 29 (95% confidence interval (CI): 18, 48) for screenees aged 55-67 years, equivalent to 3.4 (95% CI: 2.1, 5.7) overdetected Pcas per 100 screenees. The NSO decreased from 63 (95% CI: 37, 109) at the first screen to 29 (95% CI: 18, 48) at the third screen and from 43 (95% CI: 36, 52) for age 55 years to 25 (95% CI: 8, 75) at age 67 years at the first screen. In conclusion, around 3.4 cases for every 100 screened men would be overdetected during three screen rounds (~ 13 years of follow-up) in the Finnish randomized controlled trial. Elucidating the absolute RO under various scenarios makes contribution for evaluating the benefit and harm of Pca screening.

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Transcriptome sequencing reveals PCAT5 as a Novel ERG-Regulated long Noncoding RNA in prostate cancer
Castration-resistant prostate cancers (CRPC) that arise after the failure of androgen-blocking therapies cause most of the deaths from prostate cancer, intensifying the need to fully understand CRPC pathophysiology. In this study, we characterized the transcriptomic differences between untreated prostate cancer and locally recurrent CRPC. Here, we report the identification of 145 previously unannotated intergenic long noncoding RNA transcripts (lncRNA) or isoforms that are associated with prostate cancer or CRPC. Of the one third of these transcripts that were specific for CRPC, we defined a novel lncRNA termed PCAT5 as a regulatory target for the transcription factor ERG, which is activated in approximately 50% of human prostate cancer. Genome-wide expression analysis of a PCAT5-positive prostate cancer after PCAT5 silencing highlighted alterations in cell proliferation pathways. Strikingly, an in vitro validation of these alterations revealed a complex integrated phenotype affecting cell growth, migration, invasion, colony-forming potential, and apoptosis. Our findings reveal a key molecular determinant of differences between prostate cancer and CRPC at the level of the transcriptome. Furthermore, they establish PCAT5 as a novel oncogenic lncRNA in ERGpositive prostate cancers, with implications for defining CRPC biomarkers and new therapeutic interventions.

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MIR-25 modulates invasivenessand dissemination of human prostate cancer cells via regulation of αv-and α6-integrin expression
Altered microRNA (miRNA; miR) expression is associated with tumor formation and progression of various solid cancers. A major challenge in miRNA expression profiling of bulk tumors is represented by the heterogeneity of the subpopulations of cells that constitute the organ, as well as the tumor tissue. Here, we analyzed the expression of miRNAs in a subpopulation of epithelial stem/progenitor-like cells in human prostate cancer [prostate cancer stem cell (PCSC)] and compared their expression profile to more differentiated cancer cells. In both cell lines and clinical prostate cancer specimens, we identified that miR-25 expression in PCSCs was low/absent and steadily increased during their differentiation into cells with a luminal epithelial phenotype. Functional studies revealed that overexpression of miR-25 in prostate cancer cell lines and selected subpopulation of highly metastatic and tumorigenic cells ($ALDH^{high}$) strongly affected the invasive cytoskeleton, causing reduced migration in vitro and metastasis via attenuation of extravasation in vivo. Here, we show, for the first time, that miR-25 can act as a tumor suppressor in highly metastatic PCSCs by direct functional interaction with the 3′-untranslated regions of proinvasive avand a6-integrins. Taken together, our observations suggest that miR-25 is a key regulator of invasiveness in human prostate cancer through its direct interactions with αv-and α6-integrin expression. Cancer Res; 75(11); 2326-36.

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Contributors: Zoni, E., Van Der Horst, G., Van De Merbel, A. F., Chen, L., Rane, J. K., Pelger, R. C. M., Collins, A. T., Visakorpi, T., Snaar-Jagalska, B. E., Maitland, N. J., Van Der Pluijm, G.
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