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Research for a Life without Cancer

DKFZ Conference 2018

Preventive Oncology: Facing the Challenges of Cancer Prevention and Early Detection

February 15 – 16, 2018

German Cancer Research Center (DKFZ), Heidelberg, Germany

ABSTRACT BOOK

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ABSTRACT BOOK

Dear colleagues,

dear participants,

It is a great pleasure to cordially welcome you to the DKFZ CONFERENCE 2018 on Preventive Oncology: Facing the Challenges of Cancer Prevention and Early Detection.

Worldwide, each year about 14.1 million people are diagnosed with cancer and 8.2 million die from the disease. Taking population growth and aging into account, the number of new cancer diagnoses is expected to increase to 21.7 million in 2030. About 40 % of these cases could be prevented by systematic efforts to reduce lifestyle and environmental risk factors, such as smoking and poor diet, and by establishing and promoting vaccination and immunoprevention strategies. Additionally, early detection and screening approaches can substantially improve survival of cancer patients. Further advances in early detection may increase opportunities for curative treatment in the coming decades.

The DKFZ CONFERENCE 2018 on Preventive Oncology will bring together internationally leading researchers who will present their recent work and expert views in the field of cancer prevention. Five sessions will cover the broad range of ongoing research activities in the field, from identifying risk factors and developing new screening approaches to improving life with cancer. The conference will provide an excellent networking platform for researchers to identify common interests and foster cooperative projects in cancer prevention.

We wish all participants a successful conference and encourage you to use this occasion to expand your professional network.

Sincerely,

Prof. Dr. Michael Baumann

Chairman and Scientific Director
German Cancer Research Center (DKFZ)

TABLE OF CONTENTS

1. PROGRAM

THURSDAY, 15TH FEBRUARY

12:00 Registration and get-together

13:15 Welcome
Michael Baumann, *German Cancer Research Center, DE*

13:30 **INTRODUCTORY LECTURE: Ernest Hawk**, *The University of Texas MD Anderson Cancer Center, US* T01
Integrating cancer prevention through personal and public actions

TOPIC 1 PRIMARY PREVENTION: Risk factor research aiming for practical interventions

Chairs: Ute Mons, Karen Steindorf

1.1 Establishing novel interventional concepts against major cancer risk factors

14:15 **KEYNOTE: Jack Cuzick**, *Wolfson Institute of Preventive Medicine, GB* T02
Progress in cancer prevention with therapeutic agents

14:45 **Xifeng Wu**, *The University of Texas MD Anderson Cancer Center, US* T03
Precision HealthHub: to improve health and reduce cancer burden

15:05 **Augustin Scalbert**, *International Agency for Research on Cancer, FR* T04
Exploring the role of environmental risk factors for cancer through metabolomics – state of the art and prospects

15:25 **Renée Turzanski-Fortner**, *German Cancer Research Center, DE* T05
Sex steroid hormones and cancer: from etiology toward risk reduction

15:45 Coffee break and poster session

1.2 Genetic predisposition/hereditary and familial cancer

16:45 **KEYNOTE: Judy E. Garber**, *Dana-Farber Cancer Institute, US* T06
Opportunities for cancer risk-reduction in inherited breast and ovarian cancer predispositions

17:15 **Karoline Kuchenbäcker**, *University College London, GB* T07
Using prospective cohort data to estimate ovarian cancer risks for carriers of BRCA1 and BRCA2 mutations

17:35 **Mahdi Fallah**, *German Cancer Research Center, DE* T08
Risk prediction for personalized cancer prevention: colorectal cancer as an example

RECEPTION

FRIDAY, 16TH FEBRUARY

TOPIC 2

SECONDARY PREVENTION: Pushing the limits by earlier detection

Chairs: Petra Schrotz-King, Holger Sültmann

2.1 Combining molecular diagnostics with expertise in epidemiology and bioinformatics

09:00 **KEYNOTE: Stephen J. Chanock**, *National Cancer Institute, US* T09
Detectable clonal mosaicism and susceptibility to cancer

09:30 **Johanna Schleutker**, *University of Turku, FI* T10
Inherited mutations in aggressive prostate cancer

09:50 **Nicolas Wentzensen**, *National Cancer Institute, US* T11
Precision prevention of cervical cancer: addressing a global challenge

10:10 **Michael Hoffmeister**, *German Cancer Research Center, DE* T12
Precision epidemiology of colorectal cancer: the integration of molecular tumor information

10:30 Coffee break

2.2 Minimal invasive methods, including radiomics and liquid biopsies

10:45 **Ajay Goel**, *Baylor Scott & White Research Institute, US* T13
Liquid biopsy biomarkers in gastrointestinal cancers: an update

11:05 **Guillermo Barreto**, *Max-Planck-Institute for Heart and Lung Research, DE* T14
Non-invasive lung cancer diagnosis by detection of GATA6 and NKX2-1 isoforms in exhaled breath condensate

11:25 **David Bonekamp**, *German Cancer Research Center, DE* T15
Novel approaches to multi-modal imaging for early detection of cancer

11:45 **KEYNOTE: Charles Swanton**, *The Francis Crick Institute, GB* T16
Tracking cancer evolution and immune evasion

12:15 Lunch break and poster session

TOPIC 3 — TERTIARY PREVENTION: Improving life with cancer

Chair: Karen Steindorf

13:30	**KEYNOTE: Hermann Brenner**, *German Cancer Research Center, DE* **An integrated view of primary, secondary and tertiary prevention – the example of colorectal cancer**	T17
14:00	**Marjanka Schmidt**, *Netherlands Cancer Institute, NL* **The risk-prognosis continuum: What do breast cancer risk variants tell us about breast cancer outcome?**	T18
14:20	**Jenny Chang-Claude**, *German Cancer Research Center, DE* **Modifiable life-style factors that impact long-term breast cancer prognosis**	T19
14:40	**PERSPECTIVES LECTURE: Peter Boyle**, *International Prevention Research Institute, FR* **Guidelines for a healthier and longer life**	T20
15:25	Summary and wrap-up **Michael Baumann**, *German Cancer Research Center, DE*	
15:30	End of conference	

2. SPEAKERS' ABSTRACTS

T01

Ernest Hawk

The University of Texas MD Anderson Cancer Center, Houston, US

Integrating cancer prevention through personal and public actions

The global context of cancer is rapidly changing as the population ages and progressively adopts unhealthy lifestyles. Cancer prevention will be critical to address this growing challenge. It is now well established that one-third to one-half of cancer deaths are preventable in Western populations. Effective cancer prevention is applied in two domains across the lifespan: 1) evidence-based personal actions and 2) evidence-based population actions. There are at least eight actions that individuals can take to reduce cancer risk. These include avoiding tobacco and alcohol, getting plenty of physical activity, eating a plant-based diet, and adhering to recommended cancer screenings and cancer preventive vaccines. Growing evidence supports the importance of following such recommendations, demonstrating significant reductions in cancer risk (4-45 %) as well as cardiovascular (48-58 %), cancer-related (20-61 %), and all-cause (26-42 %) mortality in those adhering to cancer prevention recommendations. Complementing personal actions are strategies that organizations and societies can take to realize the promise of cancer prevention at the population level. These actions can be broadly categorized into policy, educational (professional as well as public) and clinical service delivery initiatives. Implementation and dissemination of effective population-based strategies is critical; and dissemination to those living in low-resource settings and other underserved segments of the population, who typically are in greatest need, is particularly important. Barriers to the further development of cancer prevention as a dominant strategy to reduce the cancer burden are many and varied, but must be overcome to fulfill the tremendous promise that cancer prevention offers. The objective of this presentation is to communicate, evaluate and promote evidence-based preventive actions at both the personal and population levels.

T02

Jack Cuzick

Wolfson Institute of Preventive Medicine, London, GB

Progress in cancer prevention with therapeutic agents

The development of preventive therapy for cancer is still in its infancy, and much can be learned from cardiovascular medicine, where it has now become firmly established. This is due to the existence of agents with clearly proven efficacy and minimal side-effects, such as statins for cholesterol-lowering and antihypertensive agents to control blood pressure. For cancer, with the exception of vaccination against the human papillomavirus to prevent cervix cancer, hepatitis B to prevent liver cancer, and the use of low dose aspirin to prevent gastro-intestinal cancers, most currently available efficacious medicines carry a higher side-effect profile.

Thus, it is very important to target preventive therapy to individuals who stand to benefit most.

In this talk I contrast two different types of preventive therapy – aspirin and endocrine therapy. For aspirin the benefits are seen for a range of different cancers, making identification of high risk individuals difficult. Reductions of the order of 30 % in both incidence and mortality are seen for colorectal, gastric and oesophageal cancer for long term users of low dose aspirin, and a reduction of about 10 % is estimated for breast, lung and prostate cancer.

Breast cancer is by far the commonest cancer in women, and it is an ideal disease for which to develop preventive drug therapy. For endocrine agents such as tamoxifen or the aroma-tase inhibitors, the benefit is seen only for breast cancer. Minor side effects are common, but rare but serious side effects also exist, so that the identification of high risk individuals for this cancer becomes a key priority.

Models have been developed to aid this decision and the Tyrer-Cuzick model appears to be one of the best at the moment. However newer results have shown that mammographic breast density is an important predictor and a risk score combining 88 currently identified risk SNPs adds to predictive accuracy.

T03

Xifeng Wu

The University of Texas MD Anderson Cancer Center, Houston, US

Precision HealthHub: to improve health and reduce cancer burden

The vision for a Precision HealthHub is to improve health and reduce non-communicable chronic disease burden, especially cancer burden, through big data resource building, research discovery, evidence synthesis for causal modifiable risk factors for chronic diseases and cancer, translation of science for evidence-based prevention and therapy, personalized health services, informed health policy, and developing the next generation of leaders in the field. The ultimate goal is to improve the lives of patients predisposed to or are living with chronic disease/ cancer, and the general population. A vital component of the Precision HealthHub is prediction: Whom will specific chronic disease/cancer strike? Are certain individuals more at risk and why? What can be done to identify specific chronic disease/ cancer early, prevent cancer from recurrence or thwart development of secondary primary tumors? What are the best treatment regimens for individuals with specific chronic disease/cancer? What is the future outlook for cancer survivors and how can we improve their quality of life? We envision a trans-disciplinary collaborative effort involving academic institutions, health institutions, biotech and pharmaceutical industries, government agencies, and philanthropic organizations. This level of collaboration is necessary to make efficient use of limited resources and to accelerate the discovery and translation of biomedical findings from the bench to the clinic.

T04

Augustin Scalbert

International Agency for Research on Cancer, Lyon, FR

Exploring the role of environmental risk factors for cancer through metabolomics – state of the art and prospects

Major risk factors for cancer have been identified but the causes of several types of cancer still remain largely unknown. Metabolomic approaches can be used to explore the role of environmental exposure in cancer etiology. Hundreds to thousands of exogenous and endogenous metabolites can be measured in blood or urine using highly sensitive mass spectrometry techniques. Exogenous metabolites derived from diet, drugs, contaminants or microbiota, provide direct information on exposures. Endogenous metabolites whose levels can be influenced by environmental exposures, provide information on biochemical mechanisms linking exposures to cancer. They were measured using both targeted and untargeted metabolomic approaches in case-control studies on hepatocellular carcinoma and prostate cancer nested in the European Prospective Investigation on Cancer and nutrition (EPIC) cohort. Metabolites such as amino acids, lipids, xenobiotics, were found to be associated with cancer outcomes, several years before diagnosis. Analysis by time to diagnosis showed that some of these metabolites could be subclinical markers for cancer. The same metabolomic approaches were also used in intervention or cross-sectional studies showing significant associations of some of these metabolites with lifestyle factors (diet, alcohol) and body habitus, suggesting new links between these factors and cancer. These results show the high potential of these agnostic metabolomic approaches. However, full exploitation and interpretation of these data will require improved analytical methods and bioinformatics tools. Recent progress in this rapidly moving field should lead to the identification of novel risk factors for cancers and provide new evidence on their role in cancer etiology.

T05

Renée Turzanski-Fortner

German Cancer Research Center, Heidelberg, DE

Sex steroid hormones and cancer: from etiology toward risk reduction

Endogenous sex steroid hormones are implicated in the etiology of breast, ovarian, endometrial, and colorectal cancers, among others, with recent data suggesting important differences in risk associations by disease subtype. The association between endogenous estrogens and breast cancer risk, particularly in postmenopausal women, is well established and selective estrogen receptor modulators (SERMs) and aromatase inhibitors are employed for breast cancer chemoprevention in high-risk women. However, beyond classic sex steroid hormones, other hormonally active metabolites, and mediators of hormone signaling, are of increasing interest. These include endogenous SERMs such as oxysterol 27-hydroxycholesterol, and the receptor activator of nuclear factor-kappaB (RANK)-axis.

We have investigated circulating (serum) concentrations of sex steroid hormones, as well as novel hormone-related pathways, and risk of breast and/or ovarian cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, the Scandinavian Maternity Cohorts, and international collaborations such as the Ovarian Cancer Cohort Consortium (OC3). With respect to breast cancer, ongoing work suggests an inverse association between circulating concentrations of endogenous SERM 27-hydroxycholesterol and postmenopausal breast cancer risk, and our research on sex steroids and the RANK-axis supports differential associations between hormone-related pathways and risk of estrogen (ER) and progesterone (PR) receptor-negative vs. -positive disease. Further, recent research from our group, and from others, shows that the integration of sex steroid hormones into epidemiologic risk prediction models improves discrimination between cases and non-cases, toward potential future utility for risk stratification. With respect to ovarian cancer, there is evidence for a role of hormone-related pathways in ovarian cancer risk, with differences in associations between sex steroids and histologic subtypes of the disease.

Sex steroid hormone signaling, and hormone-related pathways such as the RANK-axis and oxysterols, can be targeted pharmacologically. Further investigations considering additional novel pathways, and with detailed consideration of differential associations by disease subtype, are required.

T06

Judy Garber

Dana-Farber Cancer Institute,
Boston, US

Opportunities for cancer risk-reduction in inherited breast and ovarian cancer predispositions

Cancer risks in genetic syndromes of cancer predisposition are being quantified more precisely in large epidemiologic studies. The spectrum of risk-reduction strategies includes surgical approaches often considered too radical for groups with lower risks, especially risk reducing bilateral mastectomies with reconstruction and salpingo-oophorectomies with or without hormone replacement. One important goal of the community is the identification of risk reduction strategies that would allow carriers to at least defer these surgeries, and that are otherwise acceptable and possibly targeted. Currently active investigations include; 1) Trials of salpingectomy and delayed oophorectomy for BRCA1/2 ovarian cancer risk to defer premature menopause; 2) Examination of oral contraceptives for ovarian cancer risk reduction and effects on breast cancer risk; 3) Evaluation of post-salpingectomy/ oophorectomy hormone replacement for multiple endpoints including breast cancer risk; 4) Phase III trial of Denosumab (RANK-ligand inhibitor) for breast cancer risk reduction in BRCA1 mutation carriers (BRCA-P trial); 5) Phase II window trial of Denosumab for ovarian cancer risk reduction in BRCA1-ovarian cancer; 6) Trials of Duavee® (Bazedoxifene plus conjugated estrogens) in breast cancer risk reduction; 7) Trials of vaccine strategies in BRCA1 mutation carriers with an agent targeting h-TERT and one targeting TP53; 8) Trials of metformin in cancer risk reduction in Li Fraumeni syndrome (germline TP53 mutation). Proposed mechanisms and trial designs will be reviewed.

T07

Karoline Kuchenbäcker

University College London,
London, GB

Using prospective cohort data to estimate ovarian cancer risks for carriers of BRCA1 and BRCA2 mutations

Pathogenic mutations in BRCA1 and BRCA2 are linked to increased risks of breast, ovarian and other cancers and are frequently tested for in the clinical setting. Appropriate clinical management requires accurate age-dependent risk estimates. Recruiting sufficiently large samples of carriers of rare mutations represents a significant challenge. Strategies to increase sample size include obtaining disease status retrospectively and focusing recruitment on affected individuals. However, estimates from retrospective studies are prone to bias. Prospective cohorts where unaffected carriers of the mutation are recruited and followed over time are considered the gold standard.

We estimated ovarian cancer risk from an international collaboration, providing the largest prospective cohort of BRCA1 and BRCA2 mutation carriers. A comparison was carried out with estimates from alternative study designs. We tested whether risk varied by mutation location, degree of ovarian cancer family history and polygenic risk score (PRS) which was formed of ovarian cancer loci identified through population-based studies. In the prospective data, we did not find statistically significant associations of modifying factors which may be due to insufficient statistical power. Using retrospective data from > 30,000 affected mutation carriers, the PRS was strongly associated with ovarian cancer risk in BRCA1 carriers with a per-standard deviation hazard ratio of 1.28 (95 % CI: 1.22–1.34, p=3x10^-26) and BRCA2 carriers: 1.49 (95 % CI: 1.34–1.65, p=9x10^-14).

These risks estimates are vital for counselling. They can be used to estimate the absolute risk-reduction from preventive strategies and to inform decisions about the age to commence cancer screening. Moreover, risk-modifying factors demonstrate that more individualized risks can be estimated to enhance the clinical management.

T08

Mahdi Fallah

German Cancer Research Center, Heidelberg, DE

Risk prediction for personalized cancer prevention: colorectal cancer as an example

Screening for the early detection of cancer has been already proven to save many lives, especially for colorectal cancer. Screening guidelines usually recommend a screening modality starting from a certain age (e.g., colonoscopy from age 50) for everybody in the population, in other words, one-size-fits-all policy.

The high-risk people, such as smokers, obese people, family members of colorectal cancer patients, and individuals with certain diseases, should start screening earlier than the average-risk people, but usually they do not. The question “How many years earlier should they be screened?” either is unanswered (e.g., in those with one of many colorectal cancer related diseases like diabetes) or the answer is merely based on experts’ opinion or small studies rather than solid evidence. It is also unknown how many years the screening in those with lower risk than in the average population can be postponed to save resources for earlier screening of high-risk people.

The Risk Adapted Cancer Prevention group in the Division of Preventive Oncology in the National Center for Tumor Diseases (NCT) tries to answer these questions using the world’s largest family-disease database, which contains genealogical (family relationship) information of 12 million Swedes born after 1860s, their cancer status since 1958 (2.4 million cancer records), and their diseases diagnoses since 1960s (165 million inpatients and outpatients records).

In this talk, for the first time, evidenced-based results on optimal starting age of colorectal cancer in different individuals (with different sex, age, smoking, body mass index, and personal and family history of cancer and cancer-related diseases) will be presented. This is a step forward from cancer risk prediction to the personalized cancer prevention and optimized allocation of limited resources for cancer screening.

T09

Stephen Chanock

National Cancer Institute,
Rockville, US

Detectable clonal mosaicism and susceptibility to cancer

Clonal mosaicism arises when a post-zygotic mutational event is detectable in subpopulations of cells as an alternative genotype while not present in the germline genome. Although described in a subset of pediatric disorders, new genomic technologies have detected higher than anticipated frequencies of clonal mosaicism in adult population studies, stimulating investigation as to how clonal mosaicism could contribute to chronic human diseases, such as cancer, diabetes and neurodegenerative disorders. The risk for mosaic events increases with age. Mosaic Y loss is observed in nearly 20 % of men over 60 years of age. X chromosome mosaicism nearly always involves the inactive chromosome whereas mosaic deletions on 20q and 13q14 correspond to known regions, often mutated in myeloid neoplasms and chronic lymphocytic leukemia respectively. Early studies have characterized the spectrum of detectable mosaic alterations and have begun to investigate whether detectable mosaicism could be important as an overall biomarker for risk or in the case hematologic cancers, identification of preleukemic clones. Mounting evidence has provided new insights into possible mechanisms responsible for genome maintenance as well as identification of genomic regions most susceptible to age-related genomic instability. It is plausible that genetic mosaicism can serve as a sentinel marker for overall genomic integrity wherein an increase in detectible genetic mosaicism could be a biomarker for cancer risk. We are pursuing large studies in solid tumors and in hematologic cancers; the latter afford the opportunity to look at the dynamic of mutational steps leading to a cancer and, in doing so, could identify pre-leukemic markers. Moreover, our recent discovery of a region on chromosome 14 associated with Y chromosome mosaicism (the most common large clonal event reported so far) provides an opportunity to examine basic, underlying mechanisms of mosaicism.

T10

Johanna Schleutker

University of Turku,
Turku, FI

Inherited mutations in aggressive prostate cancer

Prostate cancer (PrCa) is a major challenge for health care worldwide. Overall, it represents the second most common cause of male cancer-related deaths in the United States, the third in the European Union, and the sixth worldwide with over 300 000 deaths per year. PrCa has a wide spectrum of clinical behavior that ranges from decades of indolence to rapid metastatic progression and lethality. PrCa is also among the most heritable of human cancers with 57 % of the inter-individual variation in risk attributed to genetic factors. Currently, there are many unmet needs in PrCa care. In screening, there are no standards. In diagnostics, biomarkers would be needed in addition to the clinical tools to identify patients in need of acute care. There are unmet needs also in prognostics: There are no means of telling at the time of diagnosis, which patients belong to the 20-30 % of men that are likely to relapse in the course of treatment. The biggest treatment challenge is determination of aggressive cancers already in early phases of the disease. Germline variants would be particularly attractive biomarkers, as they are present at the time of diagnosis and remain static despite given treatments, hormonal status or age. The so far identified risk variants using case-control designs have showed, however, little or no ability to discriminate between indolent and fatal forms of the disease. Therefore, studies contrasting patients with more and less aggressive disease, and exploring association with disease progression and prognosis, should be more effective in detecting genetic risk factors for PrCa outcome. Recent studies have given evidence to many significant genomic risk regions, and revealed several candidate genes, for example HOXB13 at 17q21.2, which show promise in reducing over-diagnosis and treatment by identifying men at high risk already at a curable state of the disease.

T11

Nicolas Wentzensen

National Cancer Institute,
Bethesda, US

Precision prevention of cervical cancer: addressing a global challenge

Cervical cancer is probably the best understood and most preventable of all major human malignancies. While cytology-based screening programs have reduced cervical cancer incidence substantially in high-resource settings, cervical cancer is still a leading cause of death in women in low-resource settings, with the incidence projected to rise. The natural history steps from HPV infection, progression to precancer, and invasion are well-characterized and uniform worldwide. Discovery of HPV as necessary cause of virtually all cervical cancers has led to two novel, highly efficacious prevention methods, prophylactic HPV vaccination to control HPV infections and HPV tests for detection of precancers. With current preventive methods, it is technically feasible to control cervical cancer globally. The speed and degree of control that is achieved depends on how vaccination and screening are implemented. Using a variety of biomarkers and diagnostic tests, we can now predict an individual's risk of cervical precancer and cancer with unprecedented precision and accuracy. In high-resource settings, HPV-based screening and risk-based management are entering clinical and public health practice. The main challenges relate to making cervical cancer prevention more efficient and less complex for screened women and providers. Due to the lack of expertise and infrastructure for cervical cancer prevention in low-resource settings, available prevention approaches need to be adapted to address specific barriers of implementation in these settings. Despite many formidable challenges, we now have the tools to make global cervical cancer control a reality.

T12

Michael Hoffmeister

German Cancer Research Center,
Heidelberg, DE

Precision epidemiology of colorectal cancer: the integration of molecular tumor information

Colorectal cancer is a heterogeneous disease developing from different pathways. Clear mechanisms to explain the association between risk factors and preventive factors and colorectal cancer remain largely unknown. The combination of epidemiological data and molecular pathological tumor analyses can provide relevant information on the associated molecular pathways. Furthermore, integration of molecular pathological markers into the current staging system has the potential to further improve the prediction of prognosis and response to therapy.

The DACHS study is a large ongoing case-control and patient cohort study from the Rhine-Neckar region in Germany with comprehensive assessment of clinical-epidemiological information and long-term follow-up of patients. For currently more than 2,000 patients, molecular-pathological analyses have been conducted in tumor tissue to subtype colorectal cancers according to major tumor markers, such as microsatellite instability, mutations in the BRAF and KRAS genes, and the CpG island methylator phenotype (CIMP). Also, for currently almost 2,500 patients, methylation information is available from array analyses in tumor tissue of more than 450,000 CpG sites. The DACHS study is participating in international consortia which allow investigations on an even larger scale.

By combining the information from the different data sources and disciplines, the MPE (“Molecular Pathological Epidemiology”) group of the Division of Clinical Epidemiology and Aging Research at DKFZ closely collaborates with experts from pathology to generate more precise and more personalized results with relevance to cancer prevention, treatment and prognosis.

T13

Ajay Goel

Baylor Scott and White Research Institute and Charles A. Sammons Cancer Center, Dallas, US

Liquid biopsy biomarkers in gastrointestinal cancers: an update

Cancer has emerged as a leading cause of mortality worldwide, claiming over 8 million lives annually. Gastrointestinal (GI) cancers account for ~ 35 % of these mortalities. Recent advances in diagnostic and treatment strategies have reduced mortality among GI cancer patients, yet a significant number of patients still develop late-stage cancer, where treatment options are inadequate. Emerging interests in 'liquid biopsies' have encouraged investigators to identify and develop clinically-relevant noninvasive genomic and epigenomic signatures that can be exploited both as biomarkers capable of detecting premalignant and early-stage cancers, and as therapeutics for targeted cancer treatment. In this context, noncoding RNAs, including microRNAs (miRNAs), which are small non-coding RNAs that are frequently dysregulated in cancers have emerged as promising entities for development as liquid biopsy biomarkers. Albeit the future looks promising, current approaches for detecting miRNAs in blood and other biofluids remain inadequate. This presentation will summarize an update on exploiting circulating miRNAs as cancer biomarkers and evaluating their potential as tissue-based, and more importantly as liquid biopsies in GI cancers.

T14

Guillermo Barreto

Max-Planck-Institute for Heart and Lung Research, Bad Nauheim, DE

Non-invasive lung cancer diagnosis by detection of GATA6 and NKX2-1 isoforms in exhaled breath condensate

Lung cancer (LC) is the leading cause of cancer-related deaths worldwide. Early LC diagnosis is crucial to reduce the high case fatality rate of this disease. In this case-control study, we developed an accurate LC diagnosis test using retrospectively collected formalin-fixed paraffin-embedded (FFPE) human lung tissues and prospectively collected exhaled breath condensates (EBCs). Following international guidelines for diagnostic methods with clinical application, reproducible standard operating procedures (SOP) were established for every step comprising our LC diagnosis method. We analyzed the expression of distinct mRNAs expressed from GATA6 and NKX2-1, key regulators of lung development. The Em/Ad expression ratios of GATA6 and NKX2-1 detected in EBCs were combined using linear kernel support vector machines (SVM) into the LC score, which can be used for LC detection. LC scorebased diagnosis achieved a high performance in an independent validation cohort. We propose our method as a non-invasive, accurate, and low-price option to complement the success of computed tomography imaging (CT) and chest X-ray (CXR) for LC diagnosis.

T15

David Bonekamp

German Cancer Research Center,
Heidelberg, DE

Novel approaches to multi-modal imaging for early detection of cancer

Multi-modal imaging allows to probe the microstructural and molecular properties of tissue, providing novel approaches for the early detection of cancer. Current advances in imaging are discussed, with a focus on prostate cancer and breast cancer, highlighting specific challenges and opportunities in improving early diagnosis. The diagnostic challenge in prostate cancer screening is accurate detection, localization and grading of cancer foci in patients with clinical suspicion for prostate cancer. The recently updated standardized clinical image interpretation by the Prostate Imaging Reporting and Data System (PI-RADS) version 2 has led to a further improvement in diagnostic accuracy. This is currently resulting in a shift in the diagnostic pathway, with MRI gaining importance and being increasingly used to guide biopsies. Prostate-specific membrane antigen (PSMA) – positron emission tomography (PET) has been demonstrated to detect microscopic lymph node and distant metastases with higher specificity than classical morphological imaging. Both in prostate and breast cancer diagnostics, diffusion MRI in its standard form, but also using specialized acquisition schemes such as diffusion kurtosis imaging (DKI) or intravoxel incoherent motion (IVIM) have recently shown specific potential for further improvement. This in combination with high-throughput techniques such as radiomics and deep learning are beginning to capture more of the information available in the multimodal imaging data.

T16

Charles Swanton

The Francis Crick Institute,
London, GB

Tracking cancer evolution and immune evasion

T17

Hermann Brenner

German Cancer Research Center,
Heidelberg, DE

An integrated view of primary, secondary and tertiary prevention – the example of colorectal cancer

Primary, secondary and tertiary prevention can all make relevant contributions to lowering the burden of cancer. Research and practice in these fields are commonly addressed by different scientific and professional groups who typically consider their field of prevention research or their field of applied prevention as the most important one. Rather than engaging in this competition, this presentation aims for an integrated view of primary, secondary and tertiary prevention from a researcher perspective, a (prevented or non-prevented) patient perspective and a societal perspective, taking colorectal cancer as an example. Prerequisites, needs and chances for eliminating most of the burden from this mostly preventable cancer are worked out.

T18

Marjanka Schmidt

Netherlands Cancer Institute,
Amsterdam, NL

The risk-prognosis continuum: what do breast cancer risk variants tell us about breast cancer outcome?

In the last decade we made a major leap forward in the discovery of new hereditary breast cancer susceptibility variants. Large scale validation studies have identified more 180 common risk variants. These add to the existing evidence of the genetic drivers of breast cancer development. While testing for high to moderate risk variants in BRCA1, BRCA2, CHEK2, and a few other genes is now common clinical practice, testing for common variants is not, because individual risk are small. However, these common breast cancer risk variants can be combined in a Polygenic Risk Score, which has shown to be able to divide women into high and low risk groups. Therefore, there is increasing awareness that such a Polygenic Risk Score may be clinically relevant in the setting of clinical genetic testing and breast cancer screening. Relevant considerations in this context are also the development of specific subtypes of breast cancer, because each subtype of breast cancer has a specific subsequent prognosis, and different prevention and treatment strategies apply. Another important aspect is the risk of development of a second breast cancer, especially within the setting of familial breast cancer. There are reasonably good estimates for increased risk of second breast cancer for BRCA1, BRCA2, and CHEK2 c.100delC mutation carriers; the impact of these genetic variants on prognosis is more debatable. Using data of the Breast Cancer Association Consortium (BCAC) and the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA), including over 100,000 breast cancer patients, we are also aiming to elucidate the impact of Polygenic Risk Scores on breast cancer outcome.

T19

Jenny Chang-Claude

German Cancer Research Center,
Heidelberg, DE

Modifiable life-style factors that impact long-term breast cancer prognosis

There is increasing evidence that modifiable lifestyle factors such as nutrition, body weight, and physical activity play an important role in long-term outcomes of breast cancer survivors, independent of prognostic factors such as tumor size, number of affected nodes, and tumor grade. Some studies have indeed shown that improvement/maintenance of preventive lifestyle factors after diagnosis, such as physical activity levels, can benefit survival. Evidence for better survival associated with modifiable lifestyle factors and biomarker profiles would provide excellent motivation for the development of tailored intervention programs that would, for example, help to modulate inflammation, which may lead to improved outcomes for breast cancer patients. We have established a unique cohort of over 3500 postmenopausal breast cancer survivors, from whom comprehensive information on lifestyle was collected at multiple time points: at recruitment, at median 6 years and 11 years later. Vital status was ascertained both at median 6 years and 11 years after diagnosis. In the breast cancer patients who survived a median of 6 years, modifiable factors such as high BMI, low physical activity in recreational sports, and smoking are all associated with poorer subsequent 5-year mortality. Furthermore, both moderate and high weight loss after diagnosis negatively impacted prognosis while maintenance of recreational sports activity after diagnosis positively impacted subsequent prognosis. Our findings from ongoing analyses provide evidence for the importance of modifiable lifestyle factors in long-term breast cancer survivors and suggest that intervention programs and control strategies to maintain or achieve a healthy lifestyle in the course of survivorship will improve survival following breast cancer diagnosis.

T20

Peter Boyle

International Prevention Research Institute, Lyon, FR

Guidelines for a healthier and longer life

Society is taking conscious steps in looking for ways to prevent serious disease and to encourage individuals to develop a healthier lifestyle. A healthy lifestyle has not been defined and it may never be possible to do so in a generic manner. There are lifestyle choices for individuals to take, many of which can lead to a healthier lifestyle. There are interventions to prevent infectious diseases by vaccination and to reduce the impact of several chronic diseases by screening, early detection and delivering appropriate therapy when chances for cure are much higher.

Tobacco causes a range of fatal conditions: chronic obstructive pulmonary disease, a variety of forms of cancer, cardiovascular diseases and diseases of the gastrointestinal tract, neurological system, eyes and skin. Alcohol use causes a variety of diseases and premature death resulting from both excessive and moderate drinking and is also associated with a wide variety of accidents and injuries, frequently during leisure activities. A healthy diet offers protection against cardiovascular disease and, perhaps, cancer. Avoiding underweight, overweight and obesity is essential for avoiding increased risks of a variety of diseases and conditions. Care is essential in the sun and use of sunbeds should be avoided. Vaccination is important to reduce, even eliminate, many infectious diseases.

There are actions that can be taken against serious chronic disease. Screening for certain cancers can be recommended but for others there is no convincing evidence of efficacy. Consideration should be given under medical advice, to prophylactic use of statins and aspirin against cancer and cardiovascular disease.

Making the correct lifestyle choices will lead to increases in healthy life expectancy as well as overall life expectancy. There is more to health than the absence of illness. The guidelines will improve health and will have a substantial impact on many aspects of quality of life.

3. POSTER ABSTRACTS

Topic 1: Primary prevention: risk factor research aiming for practical interventions

Topic 2: Secondary prevention: pushing the limits by earlier detection

Topic 3: Tertiary prevention: improving life with cancer

P01

Equity and education as means of cancer risk reduction: a focus on average Canadians and vulnerable populations

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Background: To achieve true health equity, we must take into consideration one of Canada's deadliest categories of disease – cancers. Cancer incidence varies significantly across the country, with social determinants of health playing an important role.

Objectives: To explore how an individual can reduce their risk of cancer, why cancer varies significantly across the country, and to recommend policy that can provide better and more equitable outcomes for minority populations (focus on Canadian Aboriginal communities). Applications of health promotion models are discussed.

Methods: The Canadian Cancer Society's Cancer Prevention Team undertook an extensive literature review on social determinants affecting cancer incidence. Results were shared on the website cancer.ca/prevention and presented to communities across Canada. This is an adaption of this content for poster form, with an added focus on Aboriginal populations.

Results: Aboriginal communities had worse outcomes of cancer and unique risk factors that should be considered in prevention programs. Some significant factors were food security, income, diet, land dispossession, alcohol use, smoking behaviour, and environmental pollution. There is much potential to reduce risk and improve disease outcomes.

Conclusions: With improvements in health equity and education, Canadians can enjoy a significant reduction in cancer incidence and risk. Today more than ever we understand that social determinants of health are essential for keeping populations healthy and well. The Canadian Cancer Society and recent literature suggests that applying these principles to cancer, with an equity focus, can be the next big significant improvement to public health.

What are the implications of your research to inform future policy or practice initiatives?

Recommendations include: using culturally appropriate health education sources, working with priority population to understand their needs (and unique drivers of risky behaviour), and focusing on social determinants of health to address risk factors more effectively (ex/ food insecurity or pollution on reserve).

P02

The latest evidence on obesity and breast and colorectal cancer by the WCRF/AICR Continuous Update Project

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Background: Findings have been published for 14 cancers providing insights into strength of evidence linking body fatness to 11 cancers. Updated findings for breast and colorectal cancer have just been released.

Methods: Research team searched PubMed for relevant studies as part of CUP systematic literature review. Dose-response meta-analyses were conducted and summary relative risks calculated using a random effects model. CUP panel of experts reviewed evidence and drew conclusions.

Results: Updated Breast Cancer Report included data form 119 studies, 12 million women and 260,000 breast cancer cases. Body fatness in childhood and adolescence is inversely related to risk of premenopausal breast cancer and postmenopausal breast cancer, suggesting long-term effect of body fatness at young age on breast cancer risk later in life. Findings contrast with higher breast cancer risk among postmenopausal women with greater body fatness throughout adulthood. Updated Colorectal Cancer Report included data form 99 studies, 29 million adults and 250,000 colorectal cancer cases. Greater body fatness increases colorectal cancer risk. Higher body fatness is associated with increased levels of insulin, which can promote cell growth and inhibit apoptosis, linked to greater colorectal cancer risk. Body fatness stimulates body's inflammatory response, which can promote colorectal cancer development.

Conclusions: Evidence changed CUP Panel's conclusions form 2010 Breast Cancer Report, with regard to body fatness at different life stages. The modifying effect of time of life on impact of exposure, of which obesity is an excellent case study, warrants further investigation. Findings may imply fundamental differences in etiology, confounded by complex interactions between diet, physical activity and genetics. Evidence confirmed 2011 CUP findings on colorectal cancer showing greater body fatness, marked by BMI, waist circumference and waist-hip ratio, is a cause of colorectal cancer.

P03

Healthy lifestyle reduces risk of colorectal cancer irrespective of a genetic risk score

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Background: Lifestyle factors such as alcohol consumption, body fatness, diet, physical activity and smoking are risk factors for colorectal cancer; however the combined impact of these lifestyle factors on colorectal cancer risk remains unclear. A healthy lifestyle score was generated to investigate the joint effect on colorectal cancer risk and to estimate the proportion of colorectal cancer cases attributable to lack of adherence to recommendations.

Methods: Using data from a population based case control study from Germany, we conducted multiple logistic regression analyses to examine the association between a healthy lifestyle score (derived from 5 modifiable lifestyle factors – diet, physical activity, body fatness, alcohol consumption and smoking) and colorectal cancer risk and to calculate population attributable fractions.

Results: In adjusted models, compared to participants with zero or one healthy lifestyle factor, participants with two (OR, 0.85; 95 % CI, 0.67–1.06), three (OR, 0.62; 95 % CI, 0.50–0.77), four (OR, 0.53; 95 % CI, 0.42–0.66) or five (OR, 0.33; 95 % CI, 0.26–0.43) healthy lifestyle factors showed increasingly lower risk of colorectal cancer. Associations were similar for both colon and rectal cancer. No differences were observed for subgroups stratified by genetic risk score, history of previous colonoscopy or by family history of colorectal cancer. Overall, at least 45 % (95 % CI, 35–53 %) of colorectal cancer cases were attributable to non-adherence to all five of the healthy lifestyle behaviours.

Conclusions: Our results provide strong support that a large proportion of colorectal cancer cases can be prevented through lifestyle modification irrespective of prevalent genetic risk variants. These results reinforce the importance of primary prevention of colorectal cancer.

P04

A healthy living pattern decreased risk of advanced colorectal neoplasms among screening participants in Germany

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Background: The risk of developing colorectal cancer (CRC) is associated with a wide range of modifiable risk factors such as diet and lifestyle. The individual contribution of single modifiable factors, such as alcohol consumption, physical activity, smoking, BMI or dietary components, in the development of CRC has been extensively investigated; however, evidence on their combined effect is sparse.

Objectives: The aim of this study was to analyze the association of a healthy living pattern with prevalence of advanced colorectal neoplasms among older adults in Germany.

Design: Participants of screening colonoscopy in Saarland/Germany who were enrolled in the KolosSal study (Effektivität der Früherkennungs-Koloskopie: eine Saarland-weite Studie) from 2005 until 2013 were included in this cross-sectional analysis. Dietary and lifestyle data were collected and colonoscopy results were extracted from physician's reports. The association of an a priori defined healthy living pattern (HLP) – including both dietary behavior and lifestyle, such as alcohol consumption, physical activity, smoking and BMI – with the risk of advanced colorectal neoplasms was assessed by multiple logistic regression analyses with comprehensive adjustment for potential confounders.

Results: A decreased risk of advanced colorectal neoplasms was associated with an overall healthier lifestyle and eating behavior among 14,185 participants of screening colonoscopy. A decreased risk of advanced colorectal neoplasms was seen for the highest compared to the lowest HLP group (OR 0.50; 95 % CI 0.42, 0.60). The risk of advanced colorectal neoplasms decreased by 21 % for every increase in 10 points in the HLP score (OR 0.79; 95 % CI 0.75, 0.83, $p < 0.001$).

Conclusions: The promising results highlight the effectiveness of a healthy living pattern to decrease the risk of developing colorectal neoplasms.

P05

Association of oxidative stress biomarkers with cancer risk in the German ESTHER study

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Background: Urinary 8isoprostane and oxidized guanine/guanosine concentrations are established biomarkers for lipid peroxidation and oxidative DNA/RNA damage, respectively. However, the association between pre-diagnostic levels and overall cancer incidence and incidence of cancer at specific common sites has rarely been evaluated in humans so far.

Methods: 8,888 older adults from the German ESTHER cohort were followed up for cancer incidence by cancer registry data and medical records from general practitioners. Cox regression models were adjusted for potential confounders, which were determined with directed acyclic graphs, to estimate hazard ratios (HR) and 95 % confidence intervals (95 % CI).

Results: During 14 years of follow-up, 1,334 incident cancer cases, including 203 lung, 177 colorectal, 194 breast and 218 prostate cancer cases were detected. 8-isoprostane concentration was positively associated with lung cancer, but not with cancer at the other sites. The HR (95 % CI) for the association with lung cancer was 1.69 (1.15, 2.50) for comparison of the top and bottom tertile. The association of 8-isoprostane levels with lung cancer persisted after adjustment for smoking and other risk factors but did not improve lung cancer prediction when added to a model containing age, sex and smoking. Among never and former smokers, total cancer incidence and prostate cancer incidence statistically significantly increased by 6 % and 12 % per one standard deviation increase in oxidized guanine/guanosine levels, respectively.

Conclusions: Findings from this large cohort study suggest that lipid peroxidation is involved in the development of lung cancer and that oxidative DNA/RNA damage may play a general role in cancer development in non-smokers.

P06

Targeting Nanog in colorectal tissue explant models for the evaluation of cancer prevention agents

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Background: The transcription factor Nanog is crucial for the self-renewal of cancer stem-like cells (CSCs). Nanog expression in colorectal cancer (CRC) tissue correlates with lymph node metastasis and poor prognosis. Since Nanog is not expressed in most tissues, including normal adult stem-cells, it represents a therapeutic target specific to cancer cells. Curcumin inhibits proliferation and expansion of CSCs derived from CRC and adenomas. In addition curcumin binds directly to Nanog recombinant protein. We have developed 3D in vitro explant models to further characterise the effects of curcumin on Nanog. In this work the hypothesis is tested that Nanog may be an early marker of response for CRC prevention agents.

Methods: Patient-derived CRC and adenoma tissue was cubed and treated for 24 hours with curcumin. Following treatment, explant tissues were processed for analysis by immunohistochemistry (IHC) (n=6) and flow cytometry (n=14). The effect of curcumin on CSCs (defined by expression of aldehyde dehydrogenase (ALDH) or Nanog) and differentiation (via Mucin 2 expression) was analysed using IHC. Additionally, cells expressing Nanog (Nanog) or Nanog plus proliferation marker Ki67 (Nanog/Ki67) were assessed using flow cytometry.

Results: A range of adenoma (n=5) and Dukes Stage A-C CRC (n=15) samples were studied. Following exposure to curcumin, a > 30 % reduction was observed in Nanog and Nanog/Ki67 cells. Nanog cell number was decreased in a curcumin concentration-dependent fashion in 6 samples and concentration-independently in a further 6. No response was observed in 2 samples. A reduction in Nanog and ALDH with concurrent increase in differentiation was observed via IHC in one sample.

Conclusion: Our data suggest Nanog is targeted by curcumin in adenoma and CRC tissues. Nanog may serve as a biomarker in clinical trials to identify individuals most amenable to treatment with curcumin. This concept may be applicable to the evaluation of novel CRC prevention agents.

P07

Breast cancer risk factors – awareness and attitudes of women in perimenopausal and postmenopausal age (45+) in Poland

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Background: Breast cancer is the most common malignant cancer among women in Poland. As we still don't have sufficient knowledge about origin of this disease, women's awareness and attitudes concerning few well known risk factors play a key role in prevention and early detection of breast cancer.

Material and methods: The survey was conducted from May to August 2017 among 380 women in Poland. This group included subjects which had or have breast cancer and healthy women without breast cancer in the past. Women were asked about their knowledge and attitudes concerning breast cancer. Collected data were analyzed using Microsoft Excell taking into account also place of residence and education.

Results: In the research group there were 58 % of women who had or have breast cancer and 42 % without breast cancer in the past. An average age of women was 61. Almost 88 % of them lived in the cities. Among probable breast cancer risk factors the most often indicated were gene mutations – 60 %, long-term use of hormonal contraception – 49 % and overweight and obesity – 38 %. The most rarely indicated factors were – late full time pregnancy – 12 %, childlessness – 21 % and alcohol consumption – 26 %. About 72 % of women assessed their knowledge about breast cancer as good or very good. Among these women almost 16 % respondents make breast self-examination once every 3 months, 42 % use or used in the past hormonal replacement therapy, 43 % of them drink alcohol and 86 % declared physical activity in daily life.

Conclusions: The level of knowledge as well as attitudes concerning breast cancer risk factors in the most prone group (women 45+) should be constantly improve. Results may suggest that education in this specific age group should be more efficient, dedicated only for these women and putting more effort on awareness about well-known breast cancer risk factors.

P08

European Code Against Cancer (ECAC): cancer prevention knowledge and attitudes of Polish population

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Background: It has been estimated that almost half of all cancer deaths in Europe could be avoided if everyone followed the recommendations of the European Code Against Cancer (ECAC). Little has been studied about cancer prevention knowledge and risk factors in the Polish population, where the burden of lifestyle related cancers is significant and increasing.

Material and methods: A nation-wide representative survey of 8,000 individuals was conducted in the population of Poland in 2014. Participants were inquired on lifestyle habits and on whether these habits could be related to cancer. A multivariable logistic regression analysis was carried out in which full knowledge of ECAC was treated as a binary outcome.

Results: As much as 11.51 % (936) of survey-takers had knowledge of all aspects of the European Code Against Cancer (ECAC). Knowledge of ECAC is lower in men (OR= 0.80, 95CI (0.70, 0.92)) than in women and increased with every decade of age increase. Participants who knew that particular behavior is related to cancer were less likely to eat fatty foods 4-6 times a week (OR= 0.89,95CI:0.81,0.99), less likely to often use instant foods (OR= 0.77, 95CI: 0.69, 0.86) and less likely to be overweight or obese (OR=0.70, 95CI: 0.64, 0.78), compared to those who did not know that such behavior increases cancer risk. They also less likely never underwent mammography (OR= 0.23, 95CI: 0.17, 0.31) or cervical cancer screening (OR= 0.15, 95CI: 0.12, 0.19). Those unaware of cancer risks were more likely to eat fruits and vegetables less than 4-6 times a week (OR=2.2, 95CI: 1.96, 2.52), more likely to be smokers (OR= 1.29, 95CI: 1.15, 1.45) and more likely to never use sunblock (OR= 1.43, 95CI: 1.28, 1.60).

Conclusions: Comprehensive knowledge of cancer risk factors related to lifestyle is still less than favorable in Polish population. Because those more aware of cancer risk factors are more likely to practice healthier habits, more investments should be made to educate and engage the Polish population on cancer preventive lifestyles.

P09

Black raspberry mediated colorectal cancer prevention

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It is estimated that over half of colorectal cancer (CRC) cases in the UK are preventable through lifestyle changes. Perhaps unsurprisingly, CRC cancer is strongly linked to dietary choices. High fat diets have been shown to increase the number and tumourigenic potential of stem cells and thus increase the risk of developing CRC, while diets rich in fruit, vegetables and fibre have a reduced risk. Previous clinical and preclinical CRC studies have demonstrated that the polyphenols found in black raspberries (BRBs) have chemopreventative and therapeutic effects. However, the exact mechanism for these effects remain unknown. In light of studies identifying the intestinal stem cell (ISC) as the 'cell of origin' of CRC, BRB-mediated CRC prevention may be through regulation of the normal and/or malignant ISCs.

Using a range of Wnt-deregulated mouse models of human CRC to conditionally delete Apc (the negative regulator of the Wnt signalling pathway) within the adult murine intestine we have shown that long-term exposure to dietary BRBs increases survival and reduces tumour area in Lgr5CreERT2Apcfl/fl mice, which develop macroscopic stem-cell derived Wnt-driven adenomas. Additionally, we have investigated the effects of BRB diet on ISCs in vivo and ex vivo. Specifically, BRBs partially attenuated the 'crypt-progenitor' intestinal phenotype typical of acute Apc loss and reduced the expression of stem cell marker genes in vivo, and reduced the self-renewal capacity of Apc deficient cells ex vivo using both murine and human-derived intestinal organoids. Furthermore, using RNAscope technology, we have identified a trend of reduced stem cell marker gene expression in normal tissue from CRC patients that were treated with BRBs.

Together, these data suggest that BRBs play a role in CRC chemoprevention by protectively regulating the ISC compartment. These findings further support the use of BRB intervention as a cancer-preventing tool in the context of Wnt-driven tumourigenesis.

P10

From asbestos to zinc – can we prevent mesothelioma using repurposed drugs?

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Malignant Pleural Mesothelioma (MPM) is a rare and aggressive tumour caused anthropogenically by industrial asbestos usage. MPM diagnoses are on the increase, projected to peak in the coming decades, with millions at-risk. However survival rates remain static at under one year, and both surgical and medical intervention are often unsuitable. The several-decade latency period between initial asbestos exposure and diagnosis provides an ample, but unrecognised, opportunity for preventative intervention. By repurposing drugs we hope to identify an agent that can safely be transitioned towards MPM prevention in an at-risk population.

We have identified three individual and three combinatorial treatments from an original panel of 100 off-patent, non-toxic, and tolerable repurposed drugs at achievable serum concentrations. These consistently and significantly reduce cell survival across 3 MPM cell-lines, by up to 72.59 % individually and 93.55 % combinatorially. Apoptosis and cell-cycle assays show congruent results, demonstrating increased cell death in treated cells. Moreover, having developed a PDX model from human biphasic MPM, drug-treated explants also show increased apoptosis by up to 27.0 % in response to combinatorial treatments after only 24h. This represents a far more clinically-relevant disease model, with the PDX retaining histopathological features of the original tumour, and will provide a basis for further ex vivo and eventually in vivo study.

As BAP-1 is frequently mutated in both germline and somatic MPM, we have begun testing the effects of our panel on a CRISPR-BAP-1-knockout cell-line to model early-stage disease and the possible application of our drug panel in primary prevention. However, with increasing frequency of late-stage MPM diagnoses, both secondary and tertiary preventative applications may also have a significant impact on patient survival. Through further mechanistic analyses in cancer and normal cell-lines, we hope to identify a single agent or combination that could significantly impede MPM progression and fulfil a desperate clinical need.

P11

Concentrations of sRANKL, OPG, and TRAIL in early pregnancy and risk of breast cancer following pregnancy

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Introduction: The Receptor Activator of Nuclear Factor kappa-B (RANK)-axis mediates structural changes in the breast during pregnancy in preparation for lactation, but is also implicated in mammary tumor development. The RANK-axis includes RANK, its ligand (RANKL) and osteoprotegerin (OPG). OPG is the decoy receptor for RANKL and Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL). Based on animal studies, and our own epidemiologic data, we hypothesized that relatively high circulating concentrations of RANK-axis members in early pregnancy would be associated with increased risk of breast cancer, with differential effects in estrogen (ER)+ and progesterone receptor (PR)+ and ER-/PR- disease.

Methods: A case-control study including 288 case-control sets (165 ER+/PR+, 79 ER-/PR-) was nested in the Finnish Maternity Cohort. Women eligible for this study donated a blood sample at age 40 years or younger and less than 140 days gestation in a primiparous term pregnancy. Cases were diagnosed within 10 years of the primiparous pregnancy. Serum OPG and TRAIL were measured using an electrochemiluminescence assay, and serum sRANKL (soluble RANKL) using an enzyme-linked immunosorbent assay. Risk ratios (RRs) and 95 % confidence intervals (CIs) were calculated using conditional logistic regression adjusted for gestational age at blood collection.

Results: Relatively high sRANKL concentrations were associated with increased risk of ER+/PR+ breast cancer (extreme tertiles, RR 1.71 (1.06–2.76)); this association was similar when additionally adjusting for OPG concentrations (RR 1.81 (1.10–2.98)). sRANKL concentrations were not associated with ER-/PR- disease, and we observed no associations between OPG and TRAIL and breast cancer risk.

Discussion: In line with previous observations in non-pregnant women, we provide the first evidence for an association between early pregnancy sRANKL and risk of breast cancer in the decade following pregnancy. Relatively high circulating sRANKL concentrations in early pregnancy may identify women at increased risk of breast cancer subsequent to pregnancy.

P12

Skin cancer prevention starts early in life – the 'SonnenschutzClown' preschool program

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Introduction: Skin cancer is one of the most common cancers, and the incidence of melanoma has increased rapidly. Overexposure to ultraviolet radiation is a major risk factor for the development of melanoma and explains the importance of adequate sun protection, especially in childhood. To offer a preschool program that can reduce the risk for skin cancer by establishing sun protection strategies, the University Cancer Center Dresden developed the 'SonnenschutzClown' (SC).

Methods: SC consists of a media-based educational workshop for preschool-staff as well as a free project kit (e.g. DVD with sun-protection films and songs applicable in preschool groups). The SC program combines theory-based individual as well as environmental interventions and addresses staff members, children and parents, thus realizing setting-intervention recommendations.

A pilot-study with a pre-post-control group design investigates the program effect on predeterminants of sun protection behavior in preschool-staff (N=128) within the Health Action Process Approach.

Results: Staff taking part in the SC-program state significantly higher self-efficacy-ratings ($p < .05$, $eta^2 = .15$) as well as significantly higher outcome expectancies towards sun-protection ($p < .05$, $eta^2 = .03$).

Conclusions: First results show that SC is a very promising program to promote sustainable sun-protection-strategies in preschools. With its media-based materials, SC offers high-quality information at low cost as well as an easy dissemination.

P13

Strongly enhanced colorectal cancer risk stratification by combining family history and genetic risk score

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Background and Aim: Family history (FH) and genetic risk scores (GRS) are increasingly used for risk stratification for colorectal cancer (CRC). However, they were mostly considered alternatively rather than jointly. We aimed to assess the potential of individual and joint risk stratification for CRC by FH and GRS.

Methods: A GRS was built based on the number of risk alleles in 53 previously identified single nucleotide polymorphisms among 2,363 patients with a first diagnosis of CRC and 2,198 controls in DACHS, a population-based case-control study in Germany. Associations between GRS and FH with CRC risk were quantified by multiple logistic regression.

Results: 316 cases (13.4 %) and 214 controls (9.7 %) had a first-degree relative (FDR) with CRC (adjusted odds ratio, aOR: 1.86, 95 % confidence interval, CI 1.52–2.29). A GRS in the highest decile was associated with a 3.0-fold risk increase for CRC (aOR: 3.00, 95 % CI 2.24–4.02) compared with the lowest decile. This association was tentatively more pronounced in older age groups. FH and GRS were essentially unrelated, and their joint consideration provided more accurate risk stratification than risk stratification based on each of the variables individually. For example, risk was 6.1-fold increased in the presence of both FH in a FDR and a GRS in the highest decile (aOR 6.14, 95 % CI 3.47–10.84) compared to persons without FH and a GRS in the lowest decile.

Conclusions: Both FH and the so far identified genetic variants carry essentially independent risk information and in combination provide great potential for CRC risk stratification.

P14

Lifestyle and bladder cancer: awareness of, and adherence to recommendations, and attitude toward advice

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Background: A healthy lifestyle is associated with a decreased cancer risk and could reduce the risk of cancer recurrence. We investigated whether Dutch non-muscle-invasive bladder cancer (NMIBC) patients are aware of possible risk factors for (bladder) cancer, adhere to lifestyle recommendations for cancer prevention, and do and/or would like to receive lifestyle advice after diagnosis.

Methods: A total of 975 primary NMIBC patients participating in the prospective cohort study UroLife filled out questionnaires on lifestyle habits at 6 and 12 weeks after diagnosis. At 12 weeks after diagnosis, patients completed a survey on awareness of risk factors for cancer in general and for bladder cancer, attitude toward lifestyle advice, and whether lifestyle advice was provided.

Results: Eighty-nine percent of the patients were aware that smoking is a risk factor for cancer in general, but only 44 % knew that smoking is a risk factor for bladder cancer. Overweight, physical activity, alcohol consumption, and dietary factors were mentioned as risk factors for cancer in general by only 29-66 %. Adherence to the WCRF/AICR cancer prevention guidelines varied between 35-84 %. Of the smokers, 69 % was advised to quit, while only 19 % of all patients received other lifestyle advice. More than 80 % of patients had a positive attitude toward receiving lifestyle advice from their physician.

Conclusion: NMIBC patients were quite unaware of cancer risk factors, and the degree of adherence to the cancer prevention guidelines varied widely. Patients have a positive attitude towards receiving lifestyle advice, but were not routinely informed about this by their physician.

P15

Deregulation of B cell receptor signaling and epidermal growth factor receptor signaling pathways in MGUS

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Despite our recent identification of 10 germline variants, much of genetic burden and prognostic mechanisms of monoclonal gammopathy of undetermined significance (MGUS) and its link to multiple myeloma (MM) remain unexplained. We developed a pipeline to expand our search for susceptibility markers with genome-wide pairwise interactions and subsequently identify genetic clusters and pathways to explicate mechanisms regulating MM development. We compared log-linear epistasis against improved Wellek-Ziegler statistics for pairwise interaction in case/control and case-only setup on a total of 561 cases/3769 controls to identify 26 paired risk loci. In silico biological and structural network enrichment analysis along with gene enrichment analysis with PASCAL, DEPICT and MAGENTA identified B cell receptor signaling pathway (P = 5.3E-03) downstream to allograft rejection pathway (P= 1.6E-06) and autoimmune thyroid disease pathway (P= 5.4E-06) as well as growth factor receptor regulation pathway (P= 7.1E-03) to be differentially regulated. Oncogenes ALK and CDH2 were also detected interacting with rs10251201 and rs16966921, two previously identified risk loci for MGUS. The pipeline thus developed streamline risk locus-based interaction analysis which together with genetic network and pathway enrichment helped us to identify novel pathways and variants potentially causal for MGUS and possibly for MM.

P16

Endoscopy use in different countries and public health impact on colorectal cancer mortality in Germany and the US

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Colonoscopy and sigmoidoscopy have been demonstrated to be effective in reducing colorectal cancer (CRC) incidence and mortality, and have been increasingly employed in many countries. We first conducted a systematic review to summarize colonoscopy and sigmoidoscopy use in different countries and then performed a population-based analysis to evaluate the public health impact of colonoscopy use on CRC deaths in Germany and the US.

PubMed and Web of Science were searched for articles published between 1 September 2008 and 31 October 2016. The epidemiologic metrics of attributable fraction and prevented fraction as well as the impact numbers were then calculated using colonoscopy use data from nationally representative health surveys, relative risk estimates from medical literature, and CRC death registry data.

A total of 23 studies from the US and 20 studies from other countries were included in the review. Estimates from the US were highest and continued to increase over the past decade. Endoscopy use in other countries was substantially lower except for Germany, where 55 % of the screening-eligible population reported colonoscopy utilization within 10 years in 2008–2011. Based on these utilization data, we estimated that about 36.6 % (95 % credible interval (CrI), 27.3 %–45.5 %) of CRC deaths among adults aged 55-79 years in Germany in 2008–2011 were attributable to nonuse of colonoscopy, compared with the US estimates of 38.2 % (95 % CrI, 28.6 %–47.1 %) and 33.6 % (95 % CrI, 24.8 %–42.2 %) for years 2008–2009 and 2010–2011, respectively. The proportion of CRC deaths theoretically prevented by colonoscopy use within 10 years was 30.7 % (95 % CrI, 24.8 %–35.7 %) in Germany, while in the US this proportion ranged from 29.0 % (95 % CrI, 23.4 %–33.6 %) for 2008-2009 to 33.9 % (95 % CrI, 27.4 %–39.2 %) for 2010–2011.

Recent colonoscopy use is likely to have prevented a considerable fraction of CRC mortality, and more deaths could be avoided by increasing colonoscopy utilization in the target population.

P17

Direct comparison of diagnostic performance of 9 quantitative fecal immunochemical tests for colorectal cancer screening

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A variety of fecal immunochemical tests (FITs) for hemoglobin (Hb) are used in colorectal cancer (CRC) screening. It is unclear to what extent differences in reported sensitivities and specificities reflect true heterogeneity in test performance or differences in study populations or varying pre-analytical conditions. We directly compared the sensitivity and specificity values with which 9 quantitative (laboratory-based and point of care) FITs detected advanced neoplasms (AN) in a single CRC screening study. Pre-colonoscopy stool samples were obtained from participants of screening colonoscopy in Germany from 2005 through 2010 and frozen at -80°C until analysis. The stool samples were thawed, homogenized, and used for 9 different quantitative FITs in parallel. Colonoscopy and histology reports were collected from all participants and evaluated by 2 independent, trained research assistants who were blinded to the test results. Comparative evaluations of diagnostic performance for AN were made at preset manufacturers´ thresholds (range: 2–17µg Hb/g feces), at a uniform threshold (15 µg Hb/g feces), and at adjusted thresholds yielding defined levels of specificity (99 %, 97 %, and 93 %). Of the 1667 participants who fulfilled the inclusion criteria, all cases with AN (n=216) and 300 randomly selected individuals without AN were included in the analysis. Sensitivities and specificities for AN varied widely when we used the preset thresholds (22–46 % and 86–98 %, respectively) or the uniform threshold (16–34 % and 94–98 %, respectively). Adjusting thresholds to yield a specificity of 99 %, 97 %, or 93 % resulted in almost equal sensitivities for detection of AN (14–19 %, 21 %–24 %, and 30 %–35 %, respectively) and almost equal positivity rates (2.8 %–3.4 %, 5.8 %–6.1 % and 10.1 %–10.9 %, respectively). Apparent heterogeneity in diagnostic performance of quantitative FITs can be overcome to a large extent by adjusting thresholds to yield defined levels of specificity or positivity rates. Rather than simply using thresholds recommended by the manufacturer, screening programs should choose thresholds based on intended levels of specificity and manageable positivity rates.

P18

Effectiveness of screening endoscopy in reducing colorectal cancer occurrence and death: a population-based cohort study

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Background: Colorectal cancer (CRC) is the third most common cancer worldwide. Endoscopic screening has been demonstrated to be effective in reducing CRC incidence and mortality, but the magnitude and duration of protection remain unclear. In this study we aimed to evaluate the long-term effect of endoscopy on CRC occurrence and death in a German population-based cohort study, prospectively followed over a period of 14 years.

Methods: Between 2000 and 2002, a total of 9,949 men and women aged 50–74 years were recruited into ESTHER cohort study. Information on medication, socio-demographic and lifestyle-related factors was collected from participant-reported questionnaire. Cancer occurrence and cause of death were documented by cancer registry. Associations between endoscopy use within 10 years and beyond 10 years before baseline and CRC outcomes were assessed in Cox proportional hazard models. Hazard ratios were specifically computed by gender- and age strata.

Results: Compared with no endoscopy screening, endoscopy within 10 years prior to baseline was associated with a reduced risk of CRC occurrence (Hazard ratio (HR): 0.44, 95 % confidence interval (CI): 0.28–0.70) and a reduced risk of CRC death (HR: 0.31 95 % CI: 0.12–0.78). Even stronger associations between screening endoscopy within 10 years and CRC incidence (HR: 0.36 95 % CI: 0.20–0.64) and CRC mortality (HR: 0.24 95 % CI: 0.07–0.80) were observed for participants aged over 60 years. Endoscopy use more than 10 years before baseline was also associated with a reduction in the incidence and mortality of CRC, but no statistical significance was reached.

Conclusion: This population-based cohort study suggests that endoscopy screening provides a substantial and long-lasting protective effect against CRC occurrence and death.

P19

Evolutionary trade-offs, universal cancer tasks and the function of driver mutations

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Tumor development can be seen as an evolutionary process in which mutations accumulate as tumor cells climb a cancer fitness peak in genetic space. If there were a single fitness peak, tumors should be genetically homogeneous. But genomics studies have shown that tumors are genetically heterogeneous, which suggests that there are several fitness peaks of cancer. Why are there multiple fitness peaks and what are these peaks selecting for?

The multiple fitness peaks can be explained by the theory of multi-task evolution. This theory predicts that, when cells face evolutionary trade-offs between conflicting tasks, optimal genotypes fall on low-dimensional shapes in gene expression space called polyhedra. Two tasks lead to a line, three lines to a triangle, four tasks to a tetrahedron, etc. The endpoints of the polyhedra are called archetypes and represent specialists at a certain task.

Consistent with multi-task theory, we find that solid tumors from eight cancer types fall on polyhedra. From the clinical and genetic properties of tumors closest to each archetype, we infer that these tasks are 1. lipogenesis, 2. biomass and energy, 3. cell division, 4. immune interaction, and 5. invasion and signaling. The same tasks are found across different cancer subtypes, which suggests that tumors from different cancer subtypes face evolutionary trade-offs between the same five universal cancer tasks. The task in which cancer cells specialize predicts what drugs these cells are sensitive to. Finally, different archetypes are enriched with different driver mutations. This suggests that driver mutations act as knobs to tune tumors towards different tasks.

In conclusion, multi-task evolution provides a theoretical framework to integrate mutations, gene expression and drug sensitivity in tumors.

P20

Genome-wide DNA methylation profiling in peripheral blood cells of triple-negative breast cancer patients

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Background: Triple-negative breast cancer (TNBC) represents 15 % to 20 % of all breast cancers. It is characterized by the lack of expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). It generally associates with higher relapse rate and shorter overall survival compared to other breast cancer subtypes. Recent studies shown that aberrant DNA methylation (DNAm) in peripheral blood cells was associated with risk of various solid cancers. For TNBC, little is known about DNAm changes in specific genes and large epigenome-wide association studies are lacking so far.

Methods: Epigenome-wide methylation profiling was performed in peripheral blood DNA of 233 patients diagnosed with TNBC from the breast cancer only study SKKDKFZS and 233 age-matched healthy controls from the population-based breast cancer case-control study GENICA. Methylation profiling of bisulfite converted DNA was measured using Illumina Infinium Human Methylation 450K BeadChip. A factored spectrally transformed linear mixed model ´EWASher´ was used to adjust for cell type heterogeneity and age. Validation on selected candidates was done using digital droplet PCR in an independent sample set comprising 57 TNBC cases and 124 age-matched controls from the GENICA study.

Results: Three promising CpGs comprising two hypermethylated CpGs and one hypo-methylated CpG were selected applying various selection criteria. One hypermethylated CpG is located in the promoter region of an apoptotic gene, the other in the gene body of a long noncoding RNA (lncRNA), and the hypomethylated CpG nearby a transcription factor coding gene. The hypermethylation of the CpG in the lncRNA was successfully validated. Its neighboring CpGs also showed a co-methylation correlation. The methylation inversely correlated with its expression using data from The Cancer Genome Atlas.

Conclusions: The hypermethylation of the CpG in the lcnRNA in peripheral blood may be a potential biomarker for TNBC.

P21

Familial oncogenomics: a pipeline for ranking genes and their variants in different cancer types

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Cancer predisposing genes can be detected using germline oncogenomic analyses. Advancements in the next-generation sequencing technologies boost up this approach of germline genomics to genetic counselling approach. We employed these methods in our studies of familial cancer to unravel rare clinically important variants, based on the pedigrees. Pedigree-based studies have a high discriminatory power if samples from many affected and unaffected members in each family are available. Here, we describe an upgraded version of our familial cancer variant prioritization pipeline, FCVPPv2, which is a pipeline capable of detecting rare germline variants and their corresponding cancer predisposing genes. FCVPPv2 prioritizes deleterious and regulatory germline variants, both in the coding and non-coding region for cancer families. The advantages of this approach are several-fold such as (a) reducing the large number of variants through the pedigree segregation step; (b) assessing the deleterious nature of missense variants by a combination of 12 ranking tools and 5 tools that predict genes' intolerance against deleterious mutations; (c) analysis of non-coding variants by specialized tools such as Miranda and Targetscan for 3' UTR variants, ChromHMM and SNPnexus for 5' UTR variants and FANTOM5, Funseq2 and SNPnexus for variants in enhancers and promoters; and (d) this tool can assert the rare variants with help of increasing population frequency data from public databases. Overall, we will present an overview of FCVPPv2, some of the resulting data, challenges and future prospects.

P22

A novel plasma-based assay for the differentiation of pancreatic cancer from chronic pancreatitis

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Introduction: Pancreatic ductal adenocarcinoma carcinoma (PDAC) is characterized by a poor prognosis with overall 5-year survival rates of less than 5 %. In resectable pancreatic cancer cases, the 5-year survival rates increase to 18-24 %. Therefore, an early diagnosis is key of a potentially curative treatment and screening of patients at risk is desirable. Chronic pancreatitis (CP) has a 26-fold higher risk for the development of pancreatic cancer. Established diagnostic methods such as transabdominal ultrasound and CA19-9 testing suffer from insufficient clinical performance. Therefore, the early and preferentially blood testing-based differential diagnosis of both diseases remains a clinical challenge.

Methods: For a case-control study in three tertiary referral centers 914 subjects were recruited with either PDAC (n=271, 135 thereof in resectable stages IA-IIB), CP (n=282), liver cirrhosis (n=100), or healthy as well as non-pancreatic-disease controls (n=261). Samples and data were subsequently analyzed within an initial exploratory study (n=201), a training study (n=474) and a test study (n=239). Fifty-two plasma samples from diabetic patients were analyzed from an independent study. Metabolomics data were generated from plasma and serum samples by gas-chromatography-mass spectrometry (GC-MS) and liquid-chromatography-tandem mass spectrometry (LC-MS/MS). A targeted quantitative assay (MxP® Pancreas Score) was developed that simultaneously quantifies polar and lipid metabolites after extraction and dansylation of samples by LC-MS/MS analysis.

Results: Data from MxP® Pancreas Score and additionally CA19-9 were analyzed by an elastic net algorithm and distinguished PDAC from CP with an area under the curve (AUC) of 0.92, resectable PDAC from CP with an AUC of 0.91, and PDAC from diabetic patients with an AUC of 0.93.

Conclusion: The new test has the potential to be further promoted into a laboratory developed test or an IVD assay which could greatly aid physicians in early diagnosis and treatment.

P23

DNA repair blood tests for risk assessment and early detection of lung cancer

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DNA repair is a key natural defense mechanism against cancer. In an attempt to exploit interpersonal variations in DNA repair for risk assessment and early detection of cancer, we have developed a panel of highly reproducible and robust DNA repair blood tests, for measuring the activity of OGG1, MPG, and APE1, which repair oxidative DNA damage (JNCI 104:1765–9, 2012; Carcinogenesis 35, 2763–70, 2014; Carcinogenesis 36, 982–91, 2015).

Combining enzyme activities with experimental risk estimates generates a Personalized DNA Repair Score, which measures personal DNA repair capacity of each subject. An epidemiological exploratory case-control study performed in Israel (198 subjects – 99 lung cancer patients and 99 control subjects; Cancer Prev. Res. 7, 398–406, 2014) showed that lung cancer patients have lower Personalized DNA Repair Scores than healthy people. Individuals with a DNA Repair Score in the lowest tertile of scores were 9.7-fold (95 %CI: 3.1–29.8) more likely than those in the highest tertile to belong to the lung cancer patient group. Moreover, low Personalized DNA Repair Score is a risk factor independent of, and additional to smoking, and of comparable magnitude, indicating that it can be a prognostic tool for both smokers and ex-smokers, as well as non-smokers. Results of a validation case-control study performed in the UK will be presented.

Currently we are broadening the panel of DNA repair assays by developing tests for three additional DNA repair enzymes: NEIL1, SMUG1 and TDG, with the last two adding an epigenetic component to the panel. The broader panel may potentially further improve the risk estimate performance for lung cancer, and apply to additional cancer types, possible with different contributions of each components.

The DNA repair risk biomarkers can help to identify subjects who are at high risk for lung cancer, for referral to early detection methods such as low-dose CT.

P24

Women's perceptions of risk-based breast cancer screening and prevention: a cross-cultural focus group study

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Background: Increased knowledge of breast cancer risk factors enables a shift from one-size-fits-all screening to a risk-based approach, tailoring screening policy to women's varying levels of risk. New opportunities for primary prevention of breast cancer will also arise. However, before we introduce this new heterogeneous screening and prevention programme, we need to explore its acceptability from the perspective of eligible women.

Methods: Women eligible for breast cancer screening in the Netherlands (NL), the United Kingdom (UK), and Sweden, without a previous breast cancer diagnosis were invited to take part in focus group discussions. A total of 144 women participated. Data were transcribed verbatim and analysed using thematic analysis.

Results: Analysis identified five themes across the three countries. The first theme 'knowledge burden' describes women's concern of not being able to unlearn your risk, perceiving it as either a motivator for change or a burden which may lead to stigma. The second theme 'belief in science' explains women's need to trust the science behind the risk assessment and subsequent care pathways. Theme three 'emotional impact' explores women's perceived anxiety, (false) reassurance, and other emotions that may result from risk communication. Theme four 'decision-making' highlights cultural differences in shared versus individual decision-making. Theme five 'attitude to medication' explores the controversial nature of offering preventative medication for breast cancer.

Conclusion: Women's perceptions of risk-based breast cancer screening and prevention were informed by cultural norms, common anxieties, personal experiences of breast cancer in their social network, and a lack of knowledge. This highlighted facilitators and barriers to participation, emphasising the importance of tailored educational material and risk counselling to aid informed decision-making.

P25

RNAi-based functional identification of epigenetic response modifiers impacting DNA methylation inhibitors in AML

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Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, and remains a difficult to treat disease, especially in elder patients. AML arises in hematopoietic stem and progenitor cells and frequently carries alterations in epigenetic modifiers, with up to 70 % of de novo AML cases harboring mutations in epigenetic modifiers. Furthermore, azacytidine (AZA) and decitabine (DAC), two nucleoside analogs inhibiting DNA methylation, have shown clinical efficacy in the therapy of myelodysplastic syndrome (MDS) and AML, highlighting the importance of epigenetic regulation in AML. Up to now, the mechanism of action of AZA and DAC in AML has not been fully elucidated and the response to these drugs cannot be predicted accurately.

To identify genetic response modifiers towards AZA and DAC treatment and possible biomarkers, we performed a pooled miRE-shRNA-based screen in three human leukemia cell lines using an inducible custom shRNA library targeting 670 different genes involved in epigenetic regulation. The cells were retrovirally infected with the epigenetics shRNA library. After selection of infected cells, shRNA expression was induced, and a fraction of the cells were treated with either AZA, DAC or left untreated. 10 days after shRNA induction, genomic DNA from shRNA-bearing cells was extracted, and samples for Illumina-based sequencing were generated. Altogether more than 120 pooled indexed samples were sequenced on a HiSeq4000 sequencer.

By comparing shRNA representation changes between the differentially treated groups, we identified multiple candidate genes sensitizing or protecting the leukemic cells to/from AZA and DAC treatment.

The identified candidate genes are currently validated and thus confirmed. Further analyses of the underlying mechanisms are ongoing with the aim of improving our understanding of the response to AZA and DAC treatment, to find robust biomarkers and to counteract resistance through suitable combinational therapy.

P26

The GEKKO study (Gebt dem Krebs keine Chance-Onkocheck)

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Early detection and screening have been shown to effectively reduce mortality for several cancers, such as cervical cancer and colorectal cancer.

With the NCT Research Program “Screening and Early Detection of Cancer” we intend to discover and validate biomarkers and biomarker signatures in easy-to-collect biospecimen, such as blood, urine, saliva or stool samples for early detection and risk adapted, non-invasive, personalized screening for multiple common cancers, or their precursors including colorectal cancer, other gastrointestinal cancers, lung cancer and breast cancer.

The GEKKO study is the first study at the NCT Heidelberg, where we combine a real screening study (arm A) with a prospective patient cohort study (arm B) of multiple cancer entities.

In arm A, participants undergoing screening colonoscopy are recruited in collaboration with medical practices and clinics in the Rhine-Neckar region and surrounding areas.

In arm B, we recruit, in collaboration with the University Clinics Heidelberg, newly diagnosed patients with gastrointestinal cancer, lung and breast cancer, who undergo primary treatment at the hospital.

Clinical data and biospecimen (including freshly collected tumor and adjacent tissue in arm B) are collected under highest quality standards in close cooperation with the NCT liquid and tissue biobank.

We will compare

- in arm A: participants with and without colorectal neoplasms at colonoscopy
- between arm a and b: neoplasm free participants and patients
- in arm B: patients with different outcomes

The resources established in this program will enable the development of reliable, non-invasive screening tests for population-wide screening.

P27

The DARIO study (Darmkrebsprävention – Innovative Wege am NCT)

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The risk for colorectal cancer (CRC) can be reduced by 50–70 % by endoscopic screening with detection and removal of colorectal neoplasms during screening colonoscopy or -sigmoidoscopy. Only screening colonoscopy but not -sigmoidoscopy has been offered in the German health care system for women and men aged 55 and older. Participants greatly benefit from removal of advanced adenomas that would develop into CRC in about 30 % of the carriers within 10 years. However, only 20–25 % of all eligible persons participate.

Worldwide, there is intensive research for non- or minimally invasive alternatives to endoscopic screening examinations like blood, stool or urine tests, which need to be validated in screening settings.

The DARIO study is the first population-based randomized trial within the NCT Research Program “Screening and Early Detection of Cancer” offering two different screening endoscopies conducted in a random sample of women and men at the age of 50-54 in the Rhine-Neckar region.

Participants in arm A are offered screening colonoscopy only and in arm B either screening colonoscopy or -sigmoidoscopy, all performed at the Interdisciplinary Endoscopy Center (IEZ) of the Heidelberg University Hospital.

For the first time we assess in a randomized intervention trial utilization and relevant findings (neoplasms bigger than 0.5 cm) of two endoscopic screening offers in the general population aged 50–54 years with no early detection examination for CRC within the past 5 years and concurrently set up a liquid biobank (blood, urine, stool, saliva samples) for the evaluation of biomarkers and less invasive methods for CRC screening.

P28

The role of Colorectal Cancer Associated Transcript 1, a long non-coding RNA, in tumorigenesis and metastatic process

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Colorectal cancer (CRC) represents 8 % of cancer deaths world wide and has the second-highest morbidity rate. In spite of major progress in targeted therapy and surgical techniques, majority of patients diagnosed with metastatic CRC will succumb to the disease. Colon Cancer Associated Transcript-1 (CCAT1) is a 2,628 nucleotide-long non-coding RNA, located on chromosome 8q24.21, up stream to MYC oncogene, described by our group. We showed by qRT-PCR, that CCAT1 is being significantly up-regulated in adenomatous polyps, primary tumor, normal mucosa adjacent to primary tumor, lymph node, liver and peritoneal metastases. Importantly, no expression was detected in normal colon tissue, making CCAT1 a potential cancer specific marker, especially for early cancer detection. siRNA down-regulation of CCAT1 in HT-29 Human colon cancer cell line showed significant decrease of cells proliferation by MTT assay, and cells migration by Transwell migration assay compared to un-transfected cells (MTT assay: for 24h P value=0.00001, for 48h P value=0.002. Transwell assay: 48h P value=0.01). Moreover, recently we developed specific molecular bescon – Peptide Nucleic Acid (PNA), that selectively fluorescence when hybridizes to CCAT1 on live cells. We showed complete specificity of the PNA on fresh Human biopsies taken from HIPEC surgeries that was confirmed by qRT-PCR CCAT1 expression levels. Determine CCAT1 as a specific CRC biomarker would serve in our greatest goals of promoting early cancer detection, and may play a role as a therapeutic target in drug developing.

P29

Optimal starting age of screening in family members of colorectal cancer patients

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Objective and Method: Using the follow-up data from year 1958 to 2015 in the Swedish Family-Cancer Database, the world's largest of its kind, we aimed to provide optimal starting ages of screening for men and women with different family history of colorectal cancer (CRC) using the CRC risk curve by age.

Results: A total of 12,844,692 persons were followed up to 58 years, out of which 173,796 developed CRC. The lifetime (0–79 years) cumulative risk (LCR) and standardized incidence ratio (SIR) for CRC both increased with the number of CRC-affected first- and second-degree relatives (FDRs and SDRs), and the highest risk was observed in those people with three or more CRC-affected FDRs (LCR=18 %; SIR=5, 95 % CI: 4–6) compared to those without any family history of CRC (LCR=4 %; men: 4.6 %, women: 3.5 %). Considering the initial screening age being 50 years, men and women with one affected FDR should be screened five years earlier (at age 45) than the recommended age for the general population; two FDRs, 11–12 years; three or more FDRs, 24–26 years; and only one affected SDR, two years earlier. The optimal age at initial screening would be eight years earlier for women with both one FDR and one SDR, and 12 years earlier for men with same family history. It is noteworthy that those without any CRC-affected relatives could be screened one year later than the age at initial screening in the general population.

Conclusion: This is the first time that optimal starting age of CRC screening for those with family history of CRC was calculated based on strong evidence rather than experts' opinions. Our novel findings of optimal starting age of screening help personalize the current CRC screening practice (one size fits all), and family members of CRC patients will benefit from earlier screening based on evidence-based recommendations.

P30

In vitro and in vivo modeling of gliomagenesis based on the IDH1R132H mutation

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Mutations in the isocitrate dehydrogenase 1 (IDH1) gene are the hallmark of subgroups of human brain tumors. IDH1 mutations are believed to represent an important feature for the initial development of these tumors, because they are always present in early lesions and persist during progression. The most common (~90 %) point mutation in gliomas is R132H, but there are also other genetic alterations, which are then subgroup specific, like Tumor protein 53 (TP53). The aim of this project is to build a mouse allograft model based on neural stem cells (NSCs) displaying the key properties of human astrocytomas on histological and molecular level. To reach our aim we established NSCs harboring a conditional knock-in IDH1R132H mutation and p53 knock-out.

We characterized the tumorigenic potential of cells carrying the IDH1R132H mutation only. We assume that the initiation of the mutation is not sufficient for tumor formation, but rather creates a cellular environment that enhances the susceptibility for secondary mutations finally promoting oncogenesis. To proof this hypothesis we introduced p53-/-. We were able to show that cells harboring both alterations have an enhanced tumorigenic potential. Based on these findings, we performed intracranial injections of our induced NSCs, into immuno-deficient mice. All groups were monitored with regular MRI screens in order to check for tumor outgrowth.

Cells behaved differently when we compared cells cultured a period of several months after induction (long-term) to cells that were newly induced (short-term). Long-term cultures showed significantly enhanced tumorigenic potential in vitro. Surprisingly, we saw that these cells did not produce 2-HG anymore, which is already described in human cells. Interestingly, the IDH1R132H persists in the allografts, which mirrors the human situation. Given the fact that our cell lines behave in a comparable manner, this model seems to picture the human system.

P31

Hypoxia imaging for secondary prevention in HNSCC-identifying patients at increased risk of recurrence: T2* vs. FMISO-PET

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Purpose: Patients with hypoxic head and neck squamous cell cancer (HNSCC) face inferior prognosis and are at higher risk of recurrence than patients with non-hypoxic HNSCC. Identifying the subgroup of hypoxic tumor patients could help to optimize post-treatment surveillance, e.g. by intensifying the follow-up schedule. Hypoxia imaging strategies include hypoxia PET such as 18F-misonidazole PET (FMISO-PET) and novel MRI techniques. Measurement of transverse relaxation time (T2star) has been proposed as a marker of tumor oxygenation. Purpose of the current study was to assess tumor hypoxia by FMISO-PET and MRI T2star at baseline and earl/late during radiochemotherapy (RCT) and to analyse the relation between T2star and the hypoxic tumor subvolume assessed by 18F-misonidazole PET.

Material and Methods: Baseline FDG PET and repeat FMISO PET and 3 Tesla MRI T2star were obtained in weeks 0, 2 and 5. Gross tumor volumestumor/lymph nodes (GTV-T, GTV-LN), hypoxic tumor/lymph node subvolumes (HSV-T, HSV-LN) and complementary non-hypoxic subvolumes (nonHSV-T, nonHSV-LN) were generated and mean values for T2star and SUVmean FDG PET obtained.

Results: From week 0 to 5 GTV-T and GTV-LN decreased by -56 % and -63 % and HSV-T and HSV-LN nearly completely resolved (n=10). Mean T2star signal showed no significant change for GTV-T or GTV-LN. Within HSV-T mean T2star values were smaller compared to nonHSV-T: 15.0+/-4.6 vs. 18.3+/-2.9 (p=0.051) whereas FDG SUVmean was significantly higher within hypoxic as compared to non-hypoxic regions: HSV-T 12.1+/-5.5 vs. nonHSV-T 6.1+/-2.6 and HSV-LN 10.2+/-3.9 vs. nonHSV-LN 4.7+/-1.9 (week 0, p smaller 0.026 and p smaller 0.008).

Conclusion: On MRI tumor reduction and on FMISO-PET marked reduction of tumor hypoxia (reoxygenation) was found in-line with previous findings. For the hypoxic tumor subvolume at baseline, borderline significantly smaller T2star values were found as compared to the non-hypoxic tumor subvolume, indicating a correlation between oxygenation status and T2star signal. For FMISO PET, identification of hypoxic tumors was possible for all timepoints. The role of T2star hypoxia imaging needs further elucidation.

P32

Common cancers share familial susceptibility: implications for cancer genetics and counseling

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Background: It has been proposed that susceptibility to cancer is more common in some families than in others, but the hypothesis lacks population level support. We use a novel approach by studying any cancers in large 3-generation families and thus are able to find risks even though penetrance is low.

Methods: Individuals in the nation-wide Swedish Family-Cancer Database were organized in 3 generations and the relative risk (RR) of cancer was calculated to the persons in the third generation by the numbers of cancer patients in generations 1, 2 and 3.

Results: The RRs for any cancer in generation 3 increased by numbers of affected relatives, reaching 1.61 when at least 7 relatives were diagnosed. The median patient had 2 affected relatives, and 7.0 % had 5 or more affected relatives with an RR of 1.46, which translated to an absolute risk of 21.5 % compared to 14.7 % in population by age 65 years.

Conclusions: A strong family history of cancer, regardless of tumor type, increases cancer risk of family members and calls for mechanistic explanations. Our data provide tools for counseling of cancer patients with both low and high familiar risks.

P33

Familial risks of ovarian cancer by age at diagnosis, proband type and histology

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Background: Ovarian cancer is a heterogeneous disease. Data regarding familial risks for specific proband, age at diagnosis and histology are limited. Such data can assist genetic counseling and help elucidate etiologic differences among various histologic types of ovarian malignancies.

Methods: By using the Swedish Family-Cancer Database, we estimated relative risks (RRs) for detailed family histories using a two-way comparison, which implied e.g. estimation of RRs for overall ovarian cancer when family history was histology-specific ovarian cancer, and conversely, RRs for histology-specific ovarian cancer when family history was overall ovarian cancer. Familial associations among histology-specific ovarian cancers were also explored.

Results: In families of only mother, only sisters or both mother and sisters diagnosed with ovarian cancer, cancer risks for ovary were 2.40, 2.59 and 10.40, respectively; and were higher for cases diagnosed before the age of 50 years. All histological types showed a familial risk in two-way analyses, except mucinous and sex cord-stromal tumors. Papillary serous ovarian cancers shared the most associations with other types. RRs for concordant histology were found for the following ovarian cancers: serous (2.78), papillary serous (2.43), endometrioid (3.63) and mucinous ovarian cancers (7.03). Concordant familial risks were highest only for mucinous cancer; for others, some discordant associations, such as endometrioid-papillary (29.78) and papillary-endometrioid (39.76), showed the highest RRs.

Conclusions: Familial risks are high for early-onset patients and for those with multiple affected relatives. Sharing of different histological types of ovarian cancer is likely an indication of the complexity of the underlying mechanisms.

P34

Rationale and design of the CAESAR study – a multiregional, population-based cohort study on long-term cancer survivors

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Background: Due to improving prognosis and demographic aging, the number of cancer survivors is increasing. It is estimated that there are around 4 million cancer survivors in Germany. Addressing health aspects relevant for long-term survivors (LTS) such as quality of life (QOL), late effects, quality of follow-up care has become more and more important.

Methods: The CAESAR study was initiated in 2008 in order to investigate QOL in LTS after breast, colorectal, or prostate cancer. Participants were recruited via six German population-based cancer registries (Schleswig-Holstein, Hamburg, Bremen, Münster/North Rhine-Westphalia, Rhineland-Palatinate, and Saarland). Inclusion criteria were age 20–75 years at diagnosis and a histological confirmation of breast, colorectal, or prostate cancer during the calendar period 1994–2004.

Eligible cancer survivors were asked to provide detailed information regarding their cancer survivorship experience via a postal questionnaire.

Results: Overall 6,952 out of 15,674 eligible survivors (44.4 %) could be successfully enrolled between 2008 and 2011 in the CAESAR study. A follow-up survey is currently underway in order to determine

a) QOL in LTS 14+ years after diagnosis
b) changes in QOL over a 8 years follow-up period
c) frequency of late complications, disease recurrence and progression in survivors
d) impact of baseline variables (e.g. QOL, fatigue, etc.) and life style factors (e.g. physical activity) on survival and QOL

Conclusions: The CAESAR study is one of the largest and most comprehensive studies worldwide addressing long-term cancer survivorship issues. The results of the CAESAR study will help

- to create a better knowledge regarding adverse cancer diagnosis and treatment-related outcomes such as late effects of treatment and poor quality of life,
- to develop strategies to prevent and to control these adverse cancer diagnosis and treatment-related outcomes,
- to optimize health care after cancer treatment including better follow-up care and surveillance of cancer in the long run.

P35

Effect of NLRC5 variants on CRC risk, overall survival and survival after 5-fluorouracil-based therapy

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Chronic inflammation and immune evasion are key drivers of CRC. NLRC5 is a member of the NOD-like receptor genes family and it is involved in the trans-activation of the MHC class I, playing a key role in immune-surveillance. NLRC5 expression is regulated by the IFN pathways, therefore it might also exert a role in the 5-fluorouracil (5-FU)-based therapy. The main aim of the 5-FU therapy is to eliminate myeloid-derived suppressor cells, which leads to elevated IFN gamma secretion and NLRC5 expression with subsequent activation of CD8+ T cells.

The aim of this study is to evaluate the effect of potentially functional variants in NLRC5 gene on risk, overall survival and survival after 5-FU-based therapy of CRC patients in a Czech population (1,424 cases and 1,114 controls).

SNPs within NLRC5 were selected using online bioinformatics tools such as UCSC browser, HaploReg, Regulome DB, Gtex Portal and microRNA binding site prediction tools.

We observed a marginal association between rectal cancer risk and two SNPs, rs1684575 (P=0.009) and rs3751710 (P=0.025). Furthermore, two SNPs showed a significant association with the survival outcome. All patients and metastasis-free patients at the time of diagnosis (pM0) who were homozygous carriers of the minor allele of rs27194 had a decreased overall survival (OS) as well as event-free survival (EFS) under recessive model (OSall P=0.003 and OSpM0 P=0.005, EFSpM0 P= 0.01, respectively); overall survival was also decreased for all patients and for patients with distant metastasis at the time of diagnosis who carried at least one minor allele of rs289747 (P=0.03 and P=0.003, respectively). Additionally, we tested the survival in a smaller set of CRC patients, who underwent a 5-FU-based adjuvant regimen. One polymorphism, rs12445252, was associated with OSall, OSpM0 and EFSpM0, supported by the Kaplan-Meier analysis, according to the dosage of the minor allele T (P=0.0004, P=0.0001, P=0.008, respectively).

Our results showed that polymorphisms in NLRC5 may be used as candidate prognostic markers of clinical outcome of CRC and of survival of CRC patients in response to 5-FU-treatment.

P36

Effects of resistance training on quality of life, fatigue, and sleep problems in pancreatic cancer patients

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Background: In patients with an advanced cancer disease maintaining or improving quality of life (QoL) is an important treatment goal. The beneficial effects of regular exercise on QoL, which were seen in patients with several cancer entities, have not been studied in the same way in pancreatic cancer patients. Therefore, we conducted a randomized controlled trial to assess the efficacy of a 6-month resistance training (RT) on QoL, fatigue and sleep in pancreatic cancer patients.

Methods: Pancreatic cancer patients, mostly stage II and after tumor resection during chemotherapy, were included and randomized to one of two progressive RT groups, supervised or home-based, or to usual care (CON). Both RT groups performed RT 2-times per week for 6 months. The primary outcome, physical functioning subscale of the EORTC QLQ-C30, and overall QoL, fatigue and sleep problems were assessed before the intervention, after 3 and 6 months.

Results: Out of the 65 pancreatic cancer patients, 46 patients completed the 6-months intervention period. Intention-to-treat analyses showed significant between-group mean differences (MD) for physical functioning (MD=12.5; p=0.014; effect size (ES)=0.61) in favor for the pooled RT group for changes from baseline to 3 months, as well as for the secondary outcomes overall QoL (MD=12.5; p=0.014; ES=0.73), cognitive functioning (MD=12.2; p=0.017; ES=0.61), insomnia (MD=-19.1; p=0.016; ES=0.75), and the fatigue subscales physical fatigue (MD=-2.6; p=0.020; ES=0.72), and reduced activity (MD=-2.5; p=0.031; ES=0.78). After 6 months, no between-group differences were observed. Additionally, training adherence decreased during the second 3 months of the intervention period.

Conclusions: This was the first randomized controlled RT intervention trial in pancreatic cancer patients. The findings showed improvements in QoL and related health outcomes after 3 months, but no long-lasting effects after 6 months. Given the severity of pancreatic cancer, future research need to focus on prolonging these short-term effects.

P37

Psychosocial resources: important for health-related quality of life of long-term cancer survivors?

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Background: Many long-term cancer survivors still have to adjust to possible adverse consequences of the illness or its treatment. Psychosocial resources can play an important role in this adjustment process, but research on this topic is limited, especially for very long-term survivors. The study explores, which resources are most frequently indicated by different subgroups of cancer survivors, and which role resources play for functioning and health-related quality of life (HRQL) in cancer survivors with and without recurrence.

Methods: The sample of 6,030 breast, colorectal and prostate cancer survivors (5–16 years post-diagnosis) was recruited in a German multi-regional population-based study (CAESAR). Personal resources were assessed by a 27-item checklist; HRQL was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items (EORTC QLQ-C30). General linear models were used to analyze the association of resources with HRQL.

Results: On average, cancer survivors indicated 11.4 (SD 5.1) resources as helpful. Family, activities with others, and partnership were the resources most commonly indicated overall, but frequencies varied according to age, sex, and tumor site. Physical activity, health, professional help, calmness, hope, optimism, and hobbies were most important in explaining HRQL variance. Cancer survivors with recurrence and a big resource pool were found to report similar HRQL as survivors without recurrence and a small resource pool.

Conclusions: The study underlines the importance and situational variability of personal and social resources for cancer survivors' HRQL, even years after diagnosis. Not only the availability, but also the individual perception and significance of resources should be considered in follow-up cancer care and tertiary prevention.

P38

Genome-wide DNA methylation analysis reveals a prognostic classifier for non-metastatic colorectal cancer

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Objective: Pathological staging used for the prediction of patient survival in colorectal cancer (CRC) provides only limited information.

Design: Here, a genome-wide study of DNA methylation was conducted for two cohorts of patients with non-metastatic CRC (screening cohort n=572 and validation cohort n=274). A variable screening for prognostic CpG sites was performed in the screening cohort using marginal testing based on a Cox model and subsequent adjustment of the p-values via independent hypothesis weighting using the methylation difference between 34 pairs of tumor and normal mucosa tissue as auxiliary covariate. From the 1000 CpG sites with the smallest adjusted p-value, the 20 CpG sites with the smallest Brier Score for overall survival (OS) were selected. Applying principal component analysis, we derived a prognostic methylation-based classifier for CRC patients with non-metastatic (ProMCol classifier).

Results: This classifier was associated with OS in the screening (Hazard ratio (HR)=0.51, 95 % confidence interval (CI)=0.41–0.63, p=6.2E-10) and the validation cohort (HR=0.61, 95 % CI=0.45–0.82, p=0.001). The independent validation of the ProMCol classifier revealed a reduction of the prediction error for three-year OS from 0.127, calculated only with standard clinical variables, to 0.120 combining the clinical variables with the classifier and for four-year OS from 0.153 to 0.140. All results were confirmed for disease-specific survival (DSS) with HR=0.50, 95 % CI=0.38-0.67, p=1.40E-6 in the screening cohort and with HR=0.55, 95 % CI=0.38–0.79, p=0.001 in the validation cohort. The prediction error for three-year DSS was reduced from 0.097 (calculated only with clinical variables) to 0.092 (including the ProMCol classifier) and for four-year DSS from 0.124 to 0.112.

Conclusion: The ProMCol classifier could improve the prognostic accuracy for patients with non-metastatic CRC.

P39

What prevents health care professionals from promoting physical activity to cancer patients?

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Introduction: Despite the known beneficial effects of physical activity (PA) for cancer patients, health care professionals (HCP) still do not promote it routinely. This might be due to structural barriers that prevent HCP from promoting PA to cancer patients more frequently.

Methods: 918 HCP (287 physicians working in outpatient care, 242 physicians working in inpatient care, and 389 oncology nurses) completed a comprehensive questionnaire. 9 items assessed structural barriers on a 4-point Likert Scale. Structural barriers and HCP' PA promotion behavior were analyzed using descriptive statistics. Additionally, structural barriers were tested in their prediction on the PA promotion behavior using multiple ordinal regressions, adjusted for sociodemographic variables and HCP' attitude.

Results: Across professional groups, more than 70 % of HCP indicated to promote PA to their cancer patients 'often' or 'routinely'. Highest ranked structural barrier was 'too less time per patient' (M=2.85; SD =1.02), followed by 'lack of structured and reimbursed therapeutic programs' (M=2.68; SD=0.94). The influence of structural barriers on the PA promotion behavior varied between professional groups: 'Too less time per patient' and 'lack of an expert contact person' was associated with a reduced PA promotion in two professional groups (all p less .05).

Conclusion: Although a big proportion of HCP reported to frequently promote PA, our findings suggest that HCP still perceive structural barriers. The perception and influence of structural barriers differed between professional groups, pointing to the importance to target them specifically.

P40

Epidemiological Cancer Registry Baden-Württemberg (ECR-BW): prospects for supporting prevention research

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Background: Epidemiological cancer registries are essential for cancer monitoring. Their potential is often limited by data privacy regulations, a narrow list of routinely registered data and the impossibility to collect additional data. Recent amendments of the BW Cancer Registration Act (LKrebsRG) in 2006 and 2016 provide opportunities to support academic research and may offer new avenues for prevention research.

Methods: The amendments in the LKrebsRG include changes such as:

- Compulsory reporting by treating physicians and pathologists
- Financial incentive
- Expansion of epidemiological data by inclusion of detailed clinical data (e.g. primary and subsequent therapy, follow-up information, i.e. disease recurrence)
- Improved and expanded possibilities for academic research
  - Access to aggregated and individual data
  - Cohort linkage possible
  - Direct contact and recruitment of registered patients
  - Patient reported outcome

Results:

- Completeness of registered cases increased: 62 % (2009) to 100 % (2013).
- Expansion of routine dataset
  - Completeness of epidemiological information (e.g. stage) exceeding nationwide average (54 % versus 48 %)
  - Clinical data completeness should improve
- Support of research:
  - Provision of anonymous and aggregated data for academic research
  - Cohort linkage implementation (e.g. MARIE, EPIC, LUSI, NAKO): a) to provide routine data (e.g. vital status, diagnoses, treatment), b) to support access to tissue samples (consent of patient and pathologist required)
  - Recruitment of registered patients for cancer survivorship research (e.g. Momentum, FIX)
  - Patient reported outcome: a) Collection possible for research (first proposals underway), b) Routine collection requires further legal amendments

Conclusions: Amendments of the legal framework facilitate statewide patient recruitment and cohort linkage and have strengthened the role of the ECR-BW to act as a partner for academic research. Provision of detailed treatment, follow-up and patient-reported outcome data as well as the possibility to support access to tissue-samples represents invaluable information for outcome and prevention research.

P41

DNA heterogeneity defines spatial patterns during colorectal cancer progression and metastasis

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Tumor heterogeneity between and within individual patients is a major obstacle in clinical analysis of genetic alterations for personalized therapy. To assess genetic heterogeneity in colorectal cancer (CRC), we sequenced 100 most frequently altered genes in CRC at high depth. We investigated single nucleotide variants (SNVs) and copy number variants (CNVs) in major CRC progression steps. Early stage CRC progression was examined in 30 polyps isolated during routine colonoscopy. Notably, these tumors encompassed cancerous growths side by side with their ancestral adenoma. At a later stage of metastatic CRC development 27 patients were studied, each with a primary tumor and up to four metastases.

Paired adenoma and carcinoma samples show important SNV and CNV alteration. To delve deeper into the evolutionary progression of these changes we dissected paired adenoma and carcinoma tissue. The results were then used to investigate CRC evolution. Late stages of CRC progression were characterized by clear concordance between primary and metastases samples. In contrast, heterogeneity between primary and metastatic lesions was frequently detected at CNV level. This observation prompted us to investigate intra-tumor heterogeneity in more detail, where we performed a directed disassembly of a single primary CRC tumor into 68 parts. We observed distinct CNV patterns within the tumor, while SNVs were uniform in all parts of the tumor. 3D reconstruction of this tumor revealed two CNV clusters along the proximal-distal axis of the tumor.

Our results follow genetic heterogeneity, from an early time point of tumor development in CRC to the stage of metastasis. We highlight driver genes which switch an adenomatous growth into a carcinoma and we do this in paired samples from the same lesion. CNV heterogeneity in CRC proposes the implementation of broader clinical routine analyses which take into account both DNA copy number changes as well as commonly investigated mutations.

P42

Integrating diffusion-weighted MRI in the re-irradiation treatment planning of recurrent glioblastoma

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Background/Aim: The gross tumor volume (GTV) for re-irradiation of recurrent glioblastoma (rGBM) is usually delineated based on contrast-enhanced MRI (GdMRI) or, for an increased specificity, on amino acid PET. Diffusion-weighted MRI (DWI) can reveal regions of high cellularity as surrogate for active tumor. The objective of the current study was the evaluation of localization and quality of diffusion restriction foci (GTV-ADClow) in comparison to the GTVs defined according to MRI (GTV- GdMRI) and FET-PET (GTV-PET).

Material/methods: We evaluated 41 patients, who received a fractionated stereotactic re-irradiation for rGBM and were initially treated by surgery and adjuvant radiochemotherapy. GTVs-MRI were delineated by experienced radiation oncologists. GTVs-PET were generated automatically (tumor to background ratio 1.8±0.1) and manually customized. GTVs-ADClow were manually drawn by experienced neuroradiologists and radiation oncologists on DWI data acquired by single-shot spin-echo echo-planar imaging (3D diffusion gradients, b=0, 1000 s/mm2) and ADC maps.

Results: In 73 % of patients, DWI showed areas with restricted diffusion, with GTVs-ADClow being the smallest volumes of the three GTVs. Approximately 2/3 of the GTVs-ADClow were located outside the GTVs-GdMRI and/or PET used for re-irradiation. Consequently, the evaluation of dose-volume histograms showed that GTVs-ADClow were only partially included in the irradiated high dose volume, receiving in mean 82 % of the reference dose. An adjusted GdMRI and/or PET volume taking into account restricted diffusion areas would imply an increase in GTV of 26–28 %.

Conclusion: The relevance of the target volume differences between GdMRI, FET-PET and DWI is yet to be fully understood. One can, however, suspect that planning a re-irradiation according to GdMRI and FET-PET alone may not cover the entire biologically active tumor. The clinical consequence of significant underdosage in areas of increased cellularity in DWI has still to be explored in prospective studies, such as the ongoing multicentric GLIAA trial.

P43

Longterm quality of life, problems, and needs of breast cancer survivors

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Background: Survival after non-metastasized breast cancer has substantially improved within the past decades. Thus, quality of life (QoL) after breast cancer is increasingly important. Therefore, we investigated long-term courses of QoL and persistent side-effects after breast cancer treatment.

Methods: Within two randomized exercise intervention studies with breast cancer patients during adjuvant therapy (BEATE-Study, NCT01106820, BEST-Study, NCT01468766) a 5-year follow-up was completed by 190 disease-free breast cancer survivors (response rate 79.5 %). Persisting health problems and needs were assessed by questionnaires. QoL function and symptoms were assessed with the EORTC QLQ-C30 at follow-up as well as all previous timepoints and compared with healthy reference data.

Results: At 5-year follow-up breast cancer survivors rated their global QoL and physical, social, emotional and role function on average as good as or even better than age-matched women of the general population in Germany. Yet, cancer survivors showed significantly worse EORTC scores for cognitive function and insomnia. Most commonly reported symptoms included sexual issues, sleep problems, hot flashes, pain, fatigue, memory problems, and polyneuropathy. Fatigue showed the strongest impact on global QoL. Support needs were expressed mainly for menopausal disorders (43 %), physical performance (39 %), sleep problems (38 %), arthralgia (37 %), and cognitive problems (36 %).

Discussion: On average, QoL of disease-free breast cancer survivors about 5 years post-diagnosis was largely comparable to the general population. Yet, still many survivors suffered from adverse effects. Ongoing screening and support especially regarding fatigue, sleep problems, cognitive problems, as well as menopausal/sexual symptoms should be provided during and in the years following cancer therapy to improve long-term QoL of breast cancer survivors. As the complex pattern and underlying mechanisms of fatigue, sleep disorders and cognitive function are still not well understood, we further investigate these symptoms in ongoing clinical and epidemiological trials to ultimately enable better patient-tailored treatment.

P44

The Cancer Survivorship-program ‘Aktiv in der Nachsorge’ – developing healthy lifestyle habits

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Introduction: Cancer Survivors benefit greatly from a physically active lifestyle and a healthy diet. The University Cancer Center Dresden developed the ‘Aktiv in der Nachsorge’ Nutrition Program (NP) and, in cooperation with NCT Heidelberg, the Motivational Exercise Program (MEP).

Methods: NP and MEP are designed as group programs, with the Health Action Process Approach as theoretical framework. Within the one-month NP, participants receive nutrition recommendations, are trained in self-management strategies and develop tailored nutrition plans. A pilot-study investigated self-management strategies and nutrition-knowledge in a pre-post-FU-design with 42 patients. The six-months MEP consists of 10 PA-sessions and 8 motivational-sessions. A pilot-study with a pre-post-FU-design without control group investigated the effects on objective physical fitness (PF), subjective PA and motivational determinants of PA with 42 participants.

Results: The NP significantly raised self-efficacy towards maintaining a healthy diet ($p < .05$, $eta^2 = .15$) as well as specific nutrition-knowledge ($p < .05$, $eta^2 = .17$). Participants rated goal setting (91 %) and developing a tailored nutrition plan (86 %) as particularly helpful in developing and maintaining a healthy diet.

Within the MEP, 45 % of the participants reported insufficient PA at baseline. Motivational barriers as ‘Can’t pick myself up’ (38 %) as well as barriers related to tumor disease or treatment, such as ‘Fatigue’ (23 %), were most common. Pre-post differences showed a significant increase in objective PF ($p < .01$, $r \geq .80$) as well as subjective PA ($p < .01$, $r = .71$) and a significant decrease of motivational barriers ($p < .01$, $r > .56$). The effects in increased subjective PA and reduced barriers remained stable at 3-months-FU.

Conclusions: Previous research has shown that motivational strategies such as tailoring individual plans and setting goals increase the effect of behavior change interventions. The results on hand support these findings in cancer survivors.

P45

Predicting the molecular profile of cancers based on hematoxyline and eosin stained slides using machine learning

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Background: Quick and accurate evaluation of molecular profiling is crucial for selection of treatment modality. Nevertheless, current methods for molecular profiling are limited to time consuming and costly techniques that require pathologists, specialized laboratories and advanced equipment.

Objectives: To show that the molecular profile of cancer is encoded in the morphology of the tumor and its microenvironment. The molecular profile can be obtained by exploiting the latest revolution of artificial intelligence technology to analyze patterns in standard digital hematoxylin and eosine images.

Methods: 23,000 hematoxylin and eosine stains taken from 6,000 breast cancer patients with corresponding estrogen receptor (ER) status annotations was used to train and validate a deep convolutional neural network (CNN) to predict ER status.

Results: The CNN reached an accuracy comparable to standard molecular profiling techniques, while providing real-time results at low cost. The CNN found more than 40 % cases containing morphological patterns that imply existence of ER with positive predicted value (PPV) of 97–99 %, outperforming current immunohistochemistry (IHC) techniques, and allowing a preliminary screening test for almost half the patients. Surprisingly, these morphological patterns were found in both epithelial and stromal regions.

Conclusions: Our study provides the first evidence that molecular profiling can be reliably deduced solely from the texture and structure of the tumor using artificial intelligence. Automatic computerized molecular profiling can mature to a new field in cancer diagnosis and research, with the potential to revolutionize precision medicine allowing access of targeted therapies to countries with minimal access to diagnostics facilities.

P46

Effects of exercise on sleep problems in breast cancer patients receiving radiotherapy: a randomized trial

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Sleep problems frequently affect breast cancer patients during and after treatment and reduce their quality of life. However, coping/treatment strategies are mostly unknown or understudied. Only few studies have investigated the effect of exercise on sleep quality, particularly during the course of radiotherapy.

Purpose: To assess within a large randomized controlled trial whether a 12-week exercise program starting with the radiotherapy influences sleep trajectories.

Methods: Sleep problems were assessed via self-report in 160 breast cancer patients before, during, and 3,6 and 12 months after they participated in a trial investigating 12-week resistance exercise versus a relaxation control group concomitant to adjuvant radiotherapy (BEST-Study, NCT01568766). In addition, 25 age-matched women without cancer were exercising and followed the same study protocol for comparison purposes.

Results: Ordinal logistic regression analyses revealed significant exercise intervention effects regarding the changes in sleep problems (scale: 0-100) from baseline to the end of radiotherapy (mean between-group difference (MD): -10.2, p=0.03) and to the end of intervention (MD= -10.8, p=0.01), with sleep problems decreasing in the exercise group and increasing in the control group. At 12 months, differences were still observed but were statistically non-significant (MD=-5.9, p=0.2). Further adjustment for potential confounders did not change the results. The course of sleep problems in exercising women during the exercising phase was similar in breast cancer patients and in healthy exercisers, yet, patients experienced significantly higher levels of sleep problems at all times.

Conclusions: Our large randomized exercise intervention trial confirmed results from earlier but mostly small studies that radiotherapy aggravates sleep problems in breast cancer patients and that exercise represents an effective treatment option. Given the strong link between quality of life and sleep problems, our finding that a 12-week resistance training for breast cancer patients undergoing radiotherapy reduces sleep problems is of high importance for many cancer patients.

P47

‘Still cancer patient’ self-identity is associated with healthcare use among cancer survivors: a population-based study

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Background: As more individuals are now living with cancer as a chronic illness, the concept of cancer identity is gaining attention. Limited research suggest that a self-identity as ‘cancer patient’ rather than ‘cancer survivor’ has been associated with depression and lower health-related quality of life, but hardly any research has explored this association with health care use. We aimed to investigate the association between cancer identity and health care use.

Methods: We used data from the population-based CAncEr Survivorship: A multi-Regional (CAESAR) study, conducted in collaboration between the German Cancer Research Center and six German population-based cancer registries. Survivors of breast, colorectal, and prostate cancers diagnosed in 1994–2004 completed a postal survey on self-identity, disease progression and health care use in 2009–2011. We calculated odds ratios (OR) and the 95 % confidence interval (CI) of having a patient self-identity. Analyses were adjusted for age, sex, education and cancer stage, where appropriate.

Results: Of the 6057 respondents, 15 % reported disease progression post-diagnosis. Of these, 60 % had a patient self-identity although this perception reduced with time since disease progression. Still receiving cancer treatment or aftercare was associated with patient self-identity (ORadj: 13.9, 95 % CI: 12.1–15.9). Cancer-related healthcare use in past 12 months such as visits to the general practitioner (ORadj: 2.4 95 % CI: 2.1-2.7), medical specialist (ORadj: 3.1, 95 % CI: 2.7–3.6) or non-medical practitioner (ORadj: 1.9, 95 % CI: 1.4–2.7), and hospital visits (acute care: ORadj: 3.5, 95 % CI: 2.7–4.5; University hospital: ORadj: 3.3, 95 % CI: 2.1–5.3; rehabilitation hospital: ORadj: 2.2, 95 % CI: 1.5–3.1) were associated with patient self-identity.

Conclusions: A significant proportion of cancer survivors still consider themselves as patients many years after diagnosis and this self-identity is associated with health care use. Individuals’ self-identity should be considered when exploring their cancer experience.

P48

A population-based study on quality of life in (very) long-term colorectal cancer survivors and controls

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Background: Previous research suggests an age differential in health-related quality of life (HRQL) among long-term (5–10 years post-diagnosis, LTS) colorectal cancer (CRC) survivors. Few studies have specifically addressed the association of age differentials with HRQL for very long-term CRC survivors (more than 10 years post-diagnosis, VLTS) and non-cancer controls. We aimed to assess possible deficits in HRQL of CRC-LTS and CRC-VLTS in comparison with age-matched non-cancer controls, and whether the observed pattern varies by age.

Methods: We used data from the population-based CAncEr Survivorship - A multi-Regional (CAESAR) study in collaboration with six German population-based cancer registries. Cancer survivors diagnosed in 1994–2004 and aged 20–75 years at diagnosis completed a postal survey in 2009–2011. HRQL from a representative sample of population controls was accessed from the Lebensqualität in DEeutschland (LinDE) study conducted in 2013–2014. HRQL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Core-30 questionnaire. We compared least square means of HRQL scores between CRC survivors and population controls, stratified by age (younger than 65, 65–69, 70–74, 75–79, 80 and above) and time since diagnosis. All analyses were adjusted for age, sex, and education, where appropriate.

Results: In total, 1016 CRC-LTS, 471 CRC-VLTS and 1680 LinDe respondents were included in the analyses. CRC-LTS younger than 65 years reported poorer HRQL and higher symptom scores when compared with non-cancer controls of the same age strata. CRC-VLTS reported comparable HRQL to non-cancer controls in most age groups. Both CRC-LTS and CRC-VLTS have more complaints of constipation and diarrhea than controls regardless of age. Analyses stratified by sex and cancer site (colon/rectum) showed similar results.

Conclusions: Although CRC survivors experience persistent detriments in HRQL many years after diagnosis, these effects are most felt among the younger CRC-LTS.

P49

Health-related quality of life in patients with non-muscle invasive bladder cancer: comparison to a normative population

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Background: Non-muscle-invasive bladder cancer (NMIBC) is the most common type of urinary bladder cancer. Five-year risk of recurrence is high (31–78 %), necessitating a burdensome follow-up program which may impact on health-related quality of life (HRQoL). We aimed to examine differences in HRQoL between NMIBC patients and a normative population.

Methods: Our study population consisted of primary NMIBC patients diagnosed between 2014-2016 and participating in the multicenter, prospective cohort study UroLife. Five hundred forty-nine patients (52 % response) filled out questionnaires on HRQoL (EORTC-QLQ-C30) and sociodemographic, medical and lifestyle factors at 6 weeks (T1), 3 months (T2) and 15 months (T3) after diagnosis, and were compared to an age- and sex-matched normative population (n=549) using independent t-tests.

Results: At baseline at T1, differences of small clinical importance were observed for NMIBC patients compared to the normative population for five specific domains of HRQoL: role (79 vs. 89), emotional (83 vs. 90), social functioning (86 vs. 94), insomnia (20 vs. 14), and financial difficulties (5.7 vs. 3.3). Differences in social functioning and financial difficulties persisted at T2 and T3, while levels of role and emotional functioning and insomnia were comparable to norm levels at T3. At T2 and T3, differences of small clinical importance were also observed for dyspnoea, appetite loss, and diarrhoe compared to the normative population (T3: 14 vs. 8.8, 11 vs. 2.6, and 14 vs. 4.2, respectively).

Conclusion: Our preliminary analyses show that some domains of HRQoL are lower for NMIBC patients compared to a normative population. Future analyses will be conducted to identify sociodemographic, medical and lifestyle factors that are associated with HRQoL. This may aid in developing psychosocial support and/or lifestyle interventions to improve the HRQoL of this patient group.

P50

Non-invasive metastasis prognosis from plasma metabolites in stage II colorectal cancer patients

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Metastasis is the main cause of death from colorectal cancer (CRC). Fifteen to twenty percent of stage II CRC patients develop metastasis during the course of disease. Chemotherapy treatment is effective in metastasis prevention, but clinical criteria of likely benefitting patients remain imprecise. To assess the potential of plasma metabolites to serve as biomarkers for stratification of stage II CRC patients according to metastasis risk we performed metabolic profiling of plasma samples from non-metastasized and metachronously metastasized stage II CRC patients. Metabolic profiles of 92 plasma samples from non-metastasized vs metachronously metastasized stage II CRC patients from the DACHS study were retrospectively analyzed. To identify metabolic biomarkers distinguishing non-metastasized from metachronously metastasized stage II CRC patients robust supervised classifications using decision trees and support vector machines were performed. We found that metabolic profiles are significantly different between non-metastasized and metachronously metastasized stage II CRC patients. Classification models from decision trees and support vector machines with 10-fold cross-validation resulted in average accuracy of 0.73 and 0.82, respectively, correctly predicting metachronous metastasis in stage II CRC patients. Importantly, a low number of metabolites (mean=2.8) were generally sufficient to achieve this accuracy. In summary, plasma metabolic profiles are distinct between non-metastasized and metachronously metastasized stage II CRC patients and the classification models consisting of few metabolites may have the potential to non-invasively stratify stage II CRC patients according to their risk for metachronous metastasis.













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