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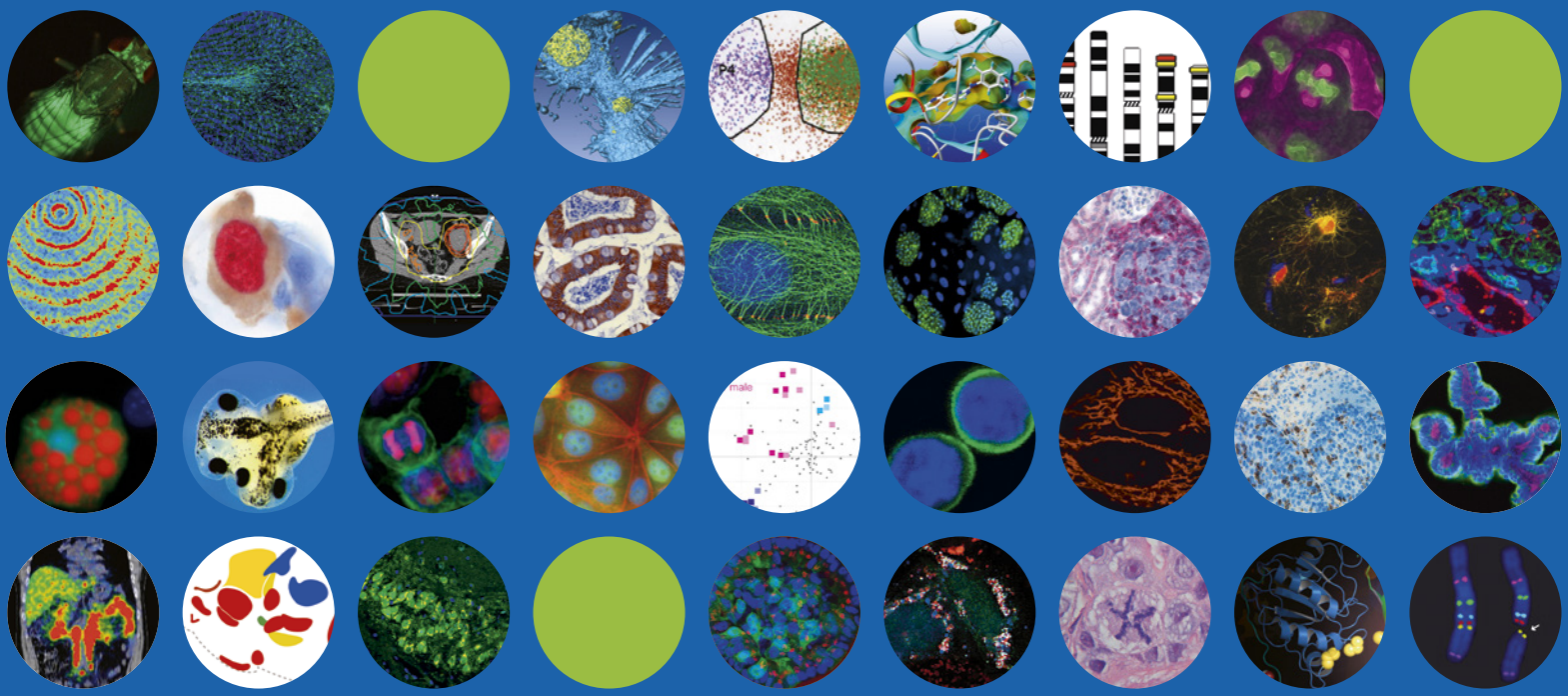
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Cancer Research at DKFZ 2016



Research Program

CANCER RISK FACTORS AND PREVENTION

RESEARCH PROGRAMS

The DKFZ covers the entire breadth of modern cancer research. Fields of research range from knowledge of the molecular basis of the development of cancer, distribution and risk factors within the population to diagnosis and treatment.

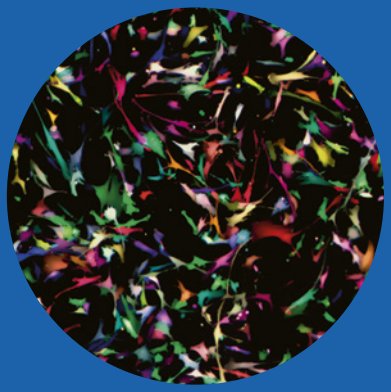
As an interdisciplinary environment, DKFZ employs scientists with qualifications in medicine, biology, biochemistry, physics, chemistry, mathematics, informatics or related issues. More than 100 division heads, group leaders and senior scientists, 200 postdocs and about 400 PhD students work together at the Center.

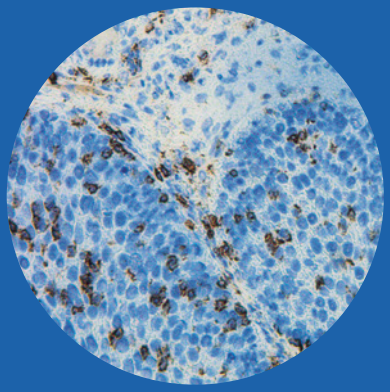
At the DKFZ, researchers benefit from intensive scientific exchange between research programs and individual groups, which serves as the basis for the internationally renowned research at the Center.

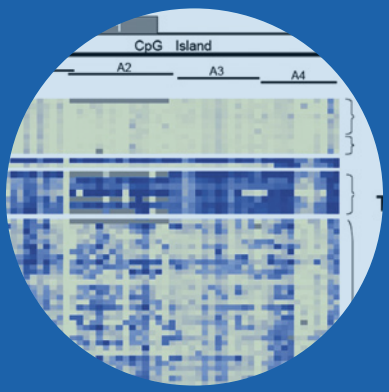
Research groups are organized into seven research programs:

- Cell Biology and Tumor Biology
- Functional and Structural Genomics
- Cancer Risk Factors and PreventionTumor Immunology
- Imaging and Radiooncology
- Infection, Inflammation and Cancer and
- Translational Cancer Research.

In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, the DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients (see also pages 150ff).



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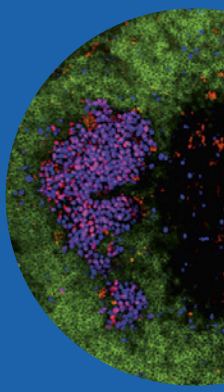
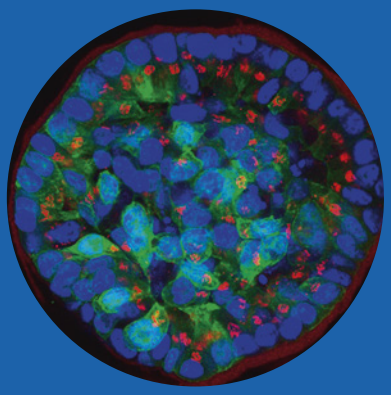
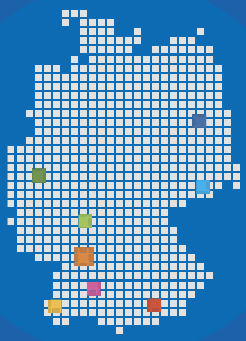
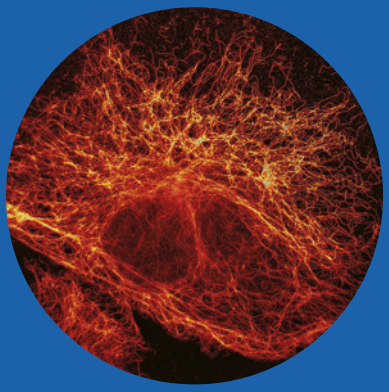
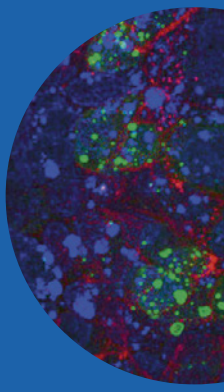








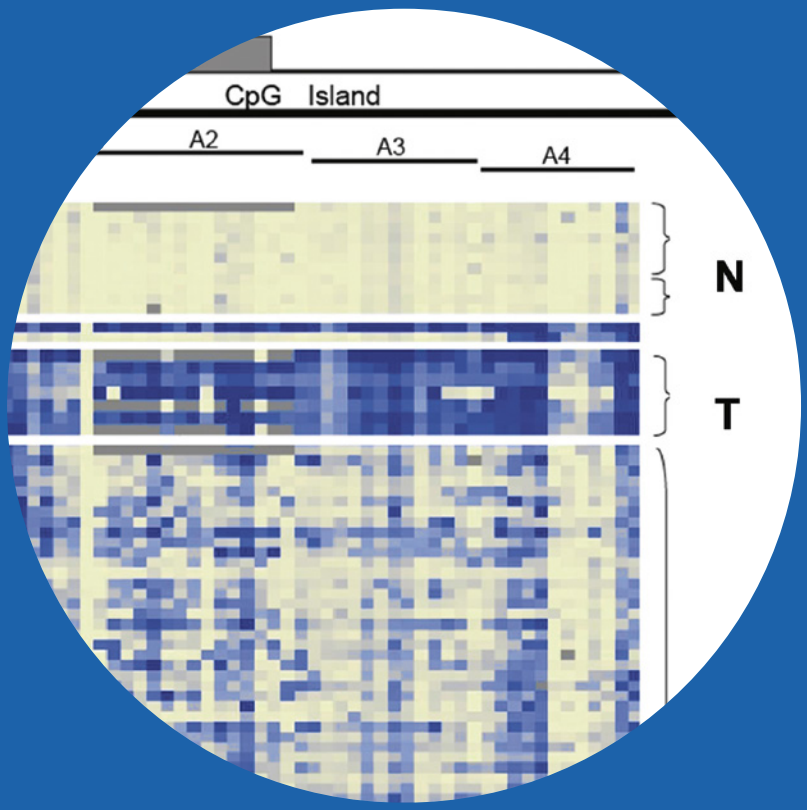


Coordinator
Prof. Dr. Rudolf Kaaks

Cancer Risk Factors and Prevention

About 210,000 people in Germany die of cancer each year. 470,000 new cancer cases are diagnosed yearly. Significant progress in prevention, diagnosis, and treatment of cancer has been made possible through recent research results in the field of molecular biology. Our Research Program is concerned with identifying risk factors (primary prevention), early detection (screening), and approaches to prevent disease progression (chemoprevention). The German Cancer Research Center occupies a leading position in the area of epidemiological studies as well as in nutrition and metabolism, biostatistics, and the application of biomarkers (characteristic biological features that are key for the prognosis or diagnosis of cancer). We expect that it may be possible to prevent up to 30 percent of new cancer cases within the next 20 to 30 years. To reach this goal, the main activities of the research program are focused on:

- integrating laboratory research, epidemiology, and clinical studies
- compiling and extending collections of biological samples and databases
- integrating genome, proteome, and biomarker research into epidemiological and clinical studies on the causes and prevention of cancer
- studies to identify causal connections such as between lifestyle, metabolism and cancer
- educational measures
- research and quality control related to novel diagnostic tests and early detection programs
- development and validation of risk stratification models
- research in the fields of biostatistics and methodological consulting



AWARDS

Prof. Hermann Brenner:
Darmkrebs-Präventionspreis 2015

Prof. Karen Steindorf:
Claudia von Schilling Award 2015

Division

Epigenomics and Cancer Risk Factors

Head: Prof. Dr. Christoph Plass

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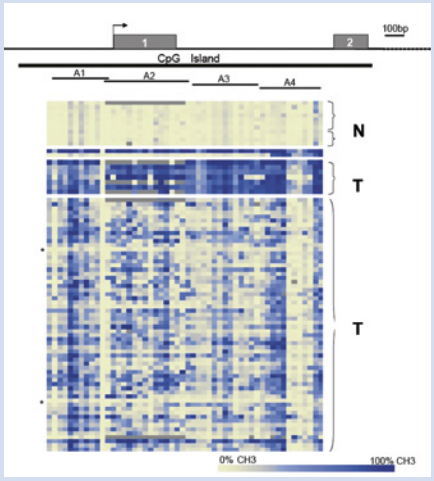
Aberrant DNA methylation is a major contributor to the development of solid tumors as well as leukemia. As an epigenetic alteration, DNA methylation does not change the sequence of a gene and thus offers the possibility for therapeutic removal of the methylation group by demethylating drugs. Deregulation of mechanisms that control the establishment of normal DNA methylation patterns leads to both extensive aberrant hypo- and hypermethylation and has been described for several human malignancies. Global DNA hypomethylation in human cancers was one of the earliest changes associated with tumor progression. Our group has shown that human malignancies are characterized by extensive promoter CpG island methylation with non-random and tumor-type specific patterns. DNA methylation changes co-occur with other epigenetic alterations such as nucleosome positioning and histone tail modifications. Our Division is interested in the molecular mechanisms underlying malignant cell growth, in particular the contribution of epigenetic alterations in this process and to determine how epigenetic and genetic alterations cooperate during tumorigenesis. We are utilizing state-of-the-art high throughput epigenomic assays (e. g. methylation arrays, next-generation sequencing on minute amounts of cells and MassARRAY) on clinical samples, cell culture and rodent tumor models.



DAPK1 mass array

FUTURE OUTLOOK:
A challenge will be to integrate epigenetic questions with other data sets in cancer research. For example, epigenetic datasets will need to be included in the profiling of cancer genomes in order to completely understand the molecular defects in cancer. Furthermore, we will need to better define the epigenomes of cell types from which cancers arise since these preexisting epigenomes will influence the progression and aggressiveness of cancers as well as influence the therapeutic outcome. Our Division will focus on six major research directions:

- Evaluation of genome-wide epigenetic patterns in tumor genomes and the cell of origin from individual cancers
- Identification of novel cancer genes and pathways targeted by epigenetic alterations
- Define the molecular mechanisms that lead to altered epigenetic patterns in cancer
- Determining the role of epigenetic pattern dynamics in differentiation of hematopoietic stem cells and other cell types
- Evaluating the role of epigenetics in the regulation of damage response
- Developing bioinformatical tools for the integrative analysis of epigenetic data

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(3) Arab K. et al. (2014). Long Noncoding RNA TARID Directs Demethylation and Activation of the Tumor Suppressor TCF21 via GADD45A. ***Mol Cell, ,*** 55(4), 604-614.
(4) Wang Q. et al. (2013). Tagmentation-based whole-genome bisulfite sequencing. ***Nat Protoc***, 8(10), 2022-2032.

Division

Cancer Epidemiology

Our Division studies the causes of cancer in population groups with the aim of identifying and, if possible, avoiding risk factors so as to prevent cancer. Our key focus is on the quantification of risks associated with lifestyle, nutrition and metabolism, and immune factors. In addition, we address the question of how lifestyle may interact with genetic susceptibility factors in cancer development, as well as in cancer survival.
On the basis of established genetic and non-genetic risk factors, we build quantitative risk models for the identification of individuals who have an increased risk of developing cancer compared to others, and who may gain increased benefit from targeted prevention measures such as regular cancer screening.
A further focus is exploring new routes for prevention and early diagnosis of cancer, as well as quality control of introduced measures. Due to their population-related approach, statistical methods and their further development are of particularly high relevance in epidemiology.
A major part of our research takes place within the setting of large-scale prospective cohort studies, such as the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Scandinavian Consortium of Maternity Cohorts. Besides these prospective studies in the general population, our Division conducts studies within large cohorts of cancer patients.

FUTURE OUTLOOK:
Studies within our various prospective cohorts are increasingly making use of modern, high-throughput "omics" technologies (metabolomics, genomics, epigenomics, next-generation sequencing) for the identification of risk factors and predictors for cancer and markers for early detection.
For future studies, our Division has a central role in the development and set-up of the "National Cohort" – a new, large-scale prospective cohort study in Germany.

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SELECTED PUBLICATIONS:
(1) Barth S. et al. (2015).Treg-mediated immune tolerance and the risk of solid cancers: Findings from EPIC-Heidelberg. ***J Natl Cancer Inst***, 107(11), pii:djv224.
(2) Fortner R.T. et al. (2014). Early pregnancy sex steroids and maternal breast cancer: a nested case-control study. ***Cancer Res***, 74(23), 6958-6967.
(3) Li K. et al. (2014).Lifestyle risk factors and residual life expectancy at age 40: a German cohort study. ***BMC Med***, 12:59.
(4) Nickels S. et al. (2013). Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. ***PLoS Genet***, 9(3):e1003284.

Division

Molecular Genetic Epidemiology

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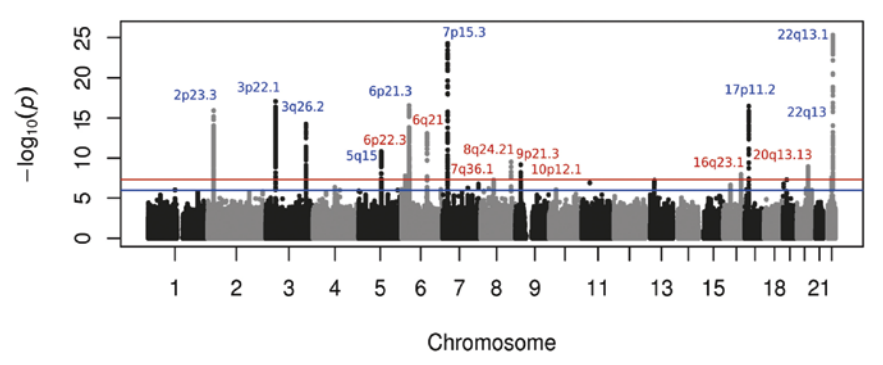
The three lines of our research include epidemiology and genetic basis of familial cancer, translational genomics of cancer and TERT promoter mutations in cancer. We have recently completed analysis of familial risks in non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma and testicular cancer. We sequence DNA from highly familial cases from Mendelian-type of cancer families in order to find out novel predisposing genes. Such families have been identified through collaborators who have collected familial/hereditary cancers. The main focus has been on colorectal cancer.

The main translational project based on a genome-wide association study (GWAS) design is on multiple myeloma in collaboration with Hartmut Goldschmidt from the University Hospital Heidelberg who heads the largest myeloma clinic in Germany. Most patients are recruited from clinical trials and GWAS data are available on 1800 patients, most also with cytogenetic (FISH) and gene expression data.

Following our discovery of TERT promoter mutations it has become evident that these alterations are common somatic events in many cancers, being associated with adverse outcomes and thus can provide prognostic information. For example in melanoma, TERT promoter mutations were associated with increased patient age, increased Breslow thickness, tumor ulceration and tumor growth rate, all markers of poor prognosis. In melanoma and glioma we have unambiguously shown that TERT promoter mutations result in increased TERT expression. We are trying to understand the genetic events leading to transformation of benign nevi to advanced melanomas. The data will be informative of the driver genetic pathways and of defining the genetic architecture of melanoma.

FUTURE OUTLOOK:

We continue to deliver clinically useful risk prediction tools based on familial risk and individual patient characteristics. In genome-wide sequencing of samples from Mendelian-type of cancer families, we aim at identifying novel high-to-moderate risk genes and characterize their population prevalence and risk profile. For translational genomics we search for susceptibility genes for cancers with a focus on the clinical relevance of germline events. In myeloma we have a possibility to test what therapeutic improvements individualized "omics" data will bring. Regarding TERT promoter mutations we will define how specific TERT promoter mutations influence clinical presentation, prognosis and therapeutic response of cancer. By genome-wide sequencing we want to follow the evolution of mutations in the course of transformation from benign nevi to advanced melanoma.



A Manhattan plot of genetic loci by chromosomal location associated with multiple myeloma given as a logarith of p-values (Mitchell et al., Nature Commun, 2015). Red peaks are new associations and blue ones were earlier described in a collaboration between DKFZ and the Heidelberg University Hospital.

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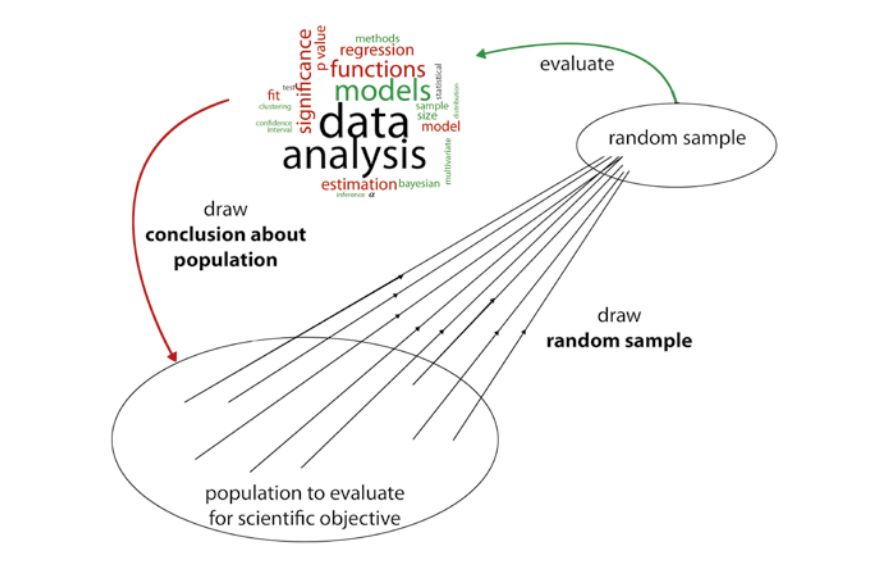
Division
Biostatistics

The main tasks of the Biostatistics Division are service and research in the field of biostatistical methods and their application in cancer research. We provide statistical support for all scientific activities of the DKFZ, from *in vitro* and animal studies to human subject research including clinical trials, thus linking the methodical research and biomedical disciplines. Our support covers experimental design, sample size estimation, data analysis and preparation of results for publication. It ranges from brief statistical consultations to long-term collaborations and covers standard statistical analysis approaches as well as the development of complex statistical methods tailored to specific questions. The ongoing evolution of novel measurement techniques and platforms, and the development of new research questions makes it necessary to continuously refine biostatistical and biomathematical methodology and to develop and implement new methods for analysis. Our current research areas reflect the requests we are confronted with from collaborators. We develop and assess efficient and valid methods for visualizing, integrating and analyzing data, in particular high-dimensional molecular data. We develop optimized biometrical designs in experimental cancer research and in clinical studies. We devise methods of quantitative risk assessment.

FUTURE OUTLOOK:
One focus of interest of our research is the evaluation of molecular data in biomarker studies. We will extend our research to find associations between clinico-pathological factors, prognosis or response to therapy with the aim of identifying diagnostic, prognostic or predictive factors. We will develop and validate statistical methods for classification and prediction using low- and high-dimensional data. The development of methods for data integration is becoming an important aspect of our work, e. g. the development of Bayesian hierarchical models for classification and prediction, which can make use of multiple data sources while properly accounting for biological inter-relations between these data. Another area of research is the development and application of statistical and stochastic models for dose-response relationships. In this context, we investigate non-linear regression models. A special focus lies on the description of cellular processes using stochastic models to understand the carcinogenesis process or the effect of toxic compounds on cell systems.



The principle of statistical inference

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SELECTED PUBLICATIONS:
(1) Benner A. et al. (2014). MDM2 promotor polymorphism and disease characteristics in chronic lymphocytic leukemia: results of an individual patient data-based meta-analysis. ***Haematologica***, 99(8), 1285-1291.
(2) Holland-Letz T. and Kopp-Schneider A. (2014). Optimal experimental designs for dose-response studies with continuous endpoints. ***Archives of Toxicolo***gy, 89(11), 2059 – 2068.
(3) Jiang X. and Kopp-Schneider A. (2014). Summarizing EC50 estimates from multiple dose-response experiments: A comparison of a meta-analysis strategy to a mixed-effects model approach. ***Biom J,*** 56(3), 493-512.
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Division

Clinical Epidemiology and Aging Research

Head: Prof. Dr. Hermann Brenner

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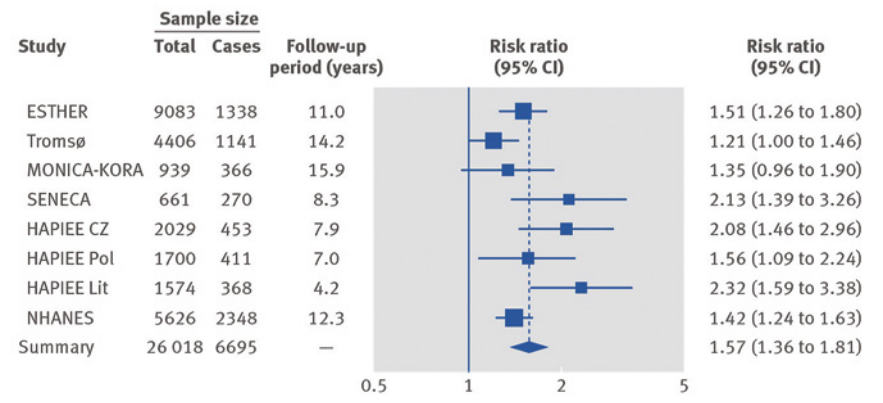
The main research areas of the Division Clinical Epidemiology and Aging Research include clinical cancer epidemiology, epidemiology of chronic age-related diseases and epidemiological methods. In the field of clinical cancer epidemiology, the group conducts large-scale epidemiological studies on new avenues of more effective cancer prevention and early detection, and on issues of the quality of medical care, prognosis and quality of life of cancer patients. Further large-scale epidemiological studies focuses on detection of risk factors, risk markers and prognostic factors of cardiovascular disease, diabetes mellitus and arthritis, thereby aiming to explore new avenues of enhanced prevention and management of these common and strongly age-related diseases. Most of the Division's studies are conducted in interdisciplinary, oftentimes international collaborations with cancer registries, and partners from both basic and clinical research. Apart from the application of the highest methodological standards in these studies, a major area of research conducted in the Division is devoted to further development and enhancement of methods in epidemiological research.

FUTURE OUTLOOK:
The Division will expand its research on early detection and screening for colorectal cancer to focus on questions of high relevance to the implementation of early detection programs at the population level. Future research in early detection and screening will also be directed towards other gastrointestinal cancers. Due to demographic aging, along with steadily increasing cancer survival rates, the number and prevalence of cancer survivors in the population will continue to increase. The Division will therefore intensify its research on additional outcomes, such as quality of life, and the occupational and social participation of cancer survivors. An area of increasing interest in aging research will be to enhance the empirical evidence for preventive and therapeutic interventions in old age. Epidemiological aging research in the Division will increasingly address integrative and functional endpoints that have received comparatively little attention so far, such as indicators of multi-morbidity and frailty, or indicators of functional limitations, as these are often more relevant for the elderly than single medical diagnoses. The Division will also provide its expertise in recruitment and follow-up of population-based cohorts, including the areas of clinical epidemiology, aging research and epidemiological methods of the National Cohort, where 200,000 older adults are to be recruited in the period from 2014 until 2018 and followed up many years afterwards.



Risk ratios of all-cause mortality for bottom versus top quintiles of 25-hydroxyvitamin D concentration in eight cohorts of older adults from various European countries and the United States (meta-analysis of individual participant data, Schöttker et al, BMJ 2014)

SELECTED PUBLICATIONS:
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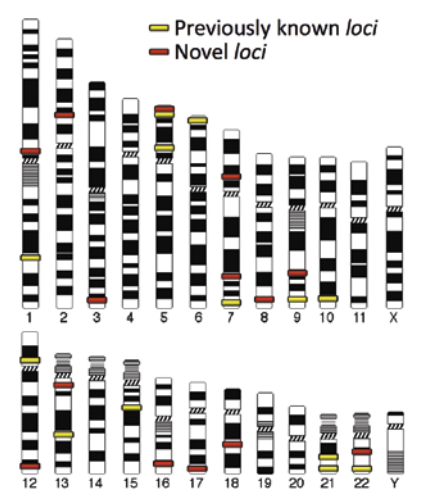
Research Group

Genomic Epidemiology

Cancer risk is influenced by inherited genetic variants, each conferring small to moderate risks of the disease. Addition of small risks determined by single genetic variants can increase or decrease cancer susceptibility significantly. Our group aims at identifying genetic variants that alter cancer risk, with the long-term goal of elaborating predictive risk models and screening strategies for cancer prevention. The objective is also to study the role of genetic variability in prognosis of cancer patients (i. e. response to treatment, overall survival or event-free survival). For these goals, we perform association studies in large-scale series of cases and controls. In particular, we focus on pancreatic cancer and multiple myeloma. For both entities we have created international consortia.



After the most recent genome-wide association studies (GWAS), done with the participation of our group (Wolpin et al., 2014; Childs et al., 2015), the number of known loci of susceptibility to pancreatic cancer has doubled.

FUTURE OUTLOOK:
We will continue to expand the consortia on pancreatic cancer and multiple myeloma, and proceed to collaborate with similar consortia for studies on specific regions/genes or genome-wide association studies. In parallel, we will study other biomarkers, such as somatic genetic alterations, telomere length, gene expression, methylation, mitochondrial copy number and metabolomics.

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SELECTED PUBLICATIONS:
(1) Campa D. et al. (2015). Risk of multiple myeloma is associated with polymorphisms within telomerase genes and telomere length. ***Int J Cancer***, 136(5), E351-8.
(2) Childs E.J. et al. (2015). Common variation at 2p13.3, 3q29, 7p13 and 17q25.1 associated with susceptibility to pancreatic cancer. ***Nat Genet***, 47(8), 911-916.


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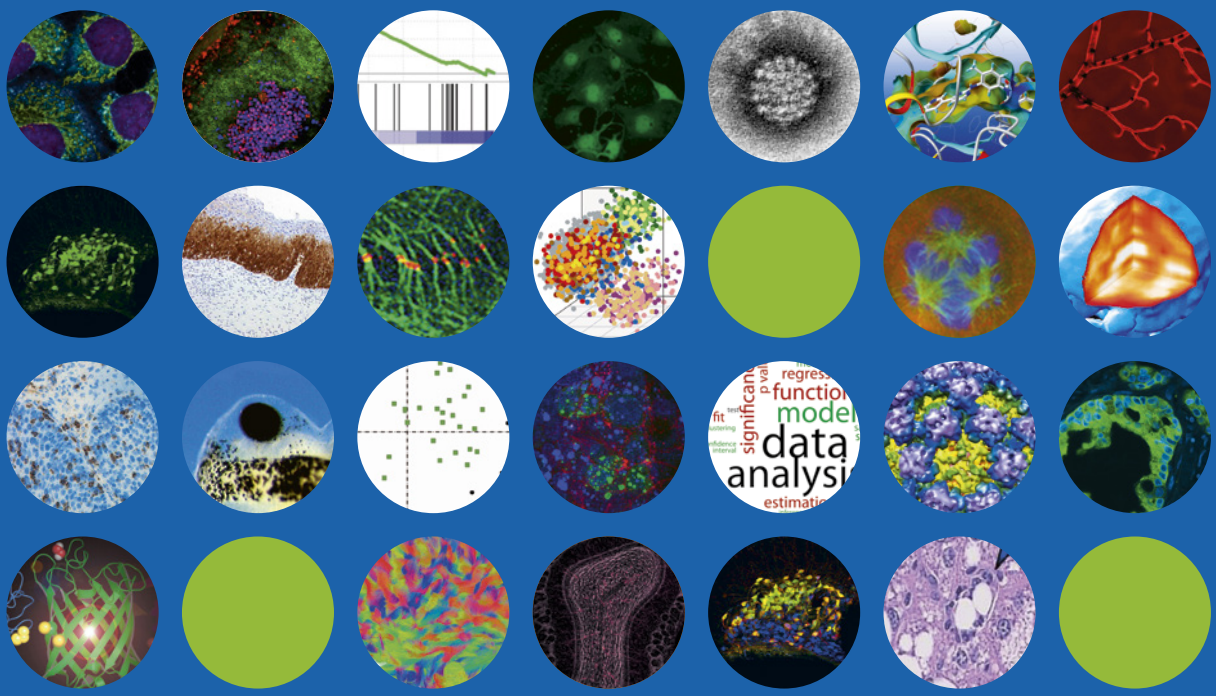

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