The unique role of the DKFZ in cancer causation and prevention research in the past 20 years has been appreciated by the scientific community and public health authorities in Germany. Selected, particularly relevant cancer risk and protective factors, together with gene-environment interactions, have been investigated by epidemiological, pathologic and molecular-toxicological methods. These methods, together with descriptive data on cancer mortality rates in Germany (Cancer Atlas of Germany), has provided a basis for rational approaches in cancer prevention. DKFZ has gained a leadership position with regard to large (EU-funded) multicenter studies, e.g. European Prospective Study into Cancer and Nutrition (EPIC) in epidemiology, nutrition, biostatistics and biomarker application; collaborative linkage with basic research in DKFZ and externally, and a new division, Molecular Genetic Epidemiology have been established.

In Germany ~330,000 persons are diagnosed annually with cancer, and ~210,000 die per year. Present approaches to molecular biology promise important advances in cancer prevention, diagnosis and therapy. The research program on Cancer Risk Factors and Cancer Prevention is directed towards the identification of risk factors (primary prevention), early diagnosis (screening) and factors that block with disease progression (chemoprevention). These are supported by research on the mechanisms of cancer development. Under realistic assumptions up to 30 % of new cancer cases could be prevented within a time frame of 20 to 30 years. To achieve this goal major efforts will be directed to:

- bring together laboratory research, epidemiology and clinical studies using a wide array of molecular, genetic and epidemiology methods;
- build up and expand biological sample and data banks and
- enhance existing activities in European and international collaborative studies.

For this purpose three divisions in the Research Program: Molecular Genetic Epidemiology (since 2002), Clinical Epidemiology (since 1999) and Genetic Alterations in Carcinogenesis (since 2000) were created and internationally reputed scientists recruited as Heads of Divisions. New priorities and directions of the Research Program C include:

- The full integration of proteomics/genomics and of sensitive biomarkers in cancer research into epidemiological and clinical studies onto cancer causes and prevention;
- Studies to establish causal relationships, and to elucidate how dietary factors modify cellular/molecular aspects of the carcinogenesis process in humans (essential for implementing rational dietary intervention studies at the population level).
- Research and quality control of new screening tests and emerging cancer screening programs.
The characterization of new safe chemopreventive agents and their mode of action, implemented by an intense interdisciplinary research network in cancer prevention, for ensuring the efficacy and safety of new prophylactic agents.

By biostatistical research and methodological consulting, provide prerequisites for up-to-date experimental/clinical study designs and analyses that include large, complex genomic and proteomic data sets.

The Division Clinical Epidemiology is primarily interested in genetic, nutritional, hormonal and occupational risk factors, and evaluation of screening. The studies involving genetic risk factors are also designed to assess gene-environment interactions. Other aspects of aetiology, including social, economic and medical, are included in all projects. Apart from the search for risk factors or causes of cancer, descriptive epidemiology, including cartographic presentation of cancer mortality, and evaluation of new statistical approaches to problems particular to observational epidemiology studies, complement the Division’s activities. Several studies are planned relating to the evaluation of screening for cancers of the breast, cervix, lung and colon, and discussions are being held over investigations of approaches to improve the outcome of cancer treatments.

The task of the Unit of Environmental Epidemiology is to investigate the influence of several environmental factors on the etiology of different cancer types. Electromagnetic fields, physical activity and occupational hazards, but also the association with viral infections are some of these factors. Large investigations concerning the relation between possible risk factors and person-specific conditions are performed within classic epidemiological approaches (case-control studies, cohort studies etc.). Furthermore, extended investigations are performed on the relationship between presumed risk factors and somatic conditions, i.e. biomarkers, host-factors, genetic predispositions and co-mobility. Likewise, the influence of other environmental factors, e.g., nutrition, physical activity and smoking, is analyzed. Due to its population-based approach, application and improvement of statistical methods in epidemiology are of special importance. Several different projects have been established in order to investigate these research tasks: the current main emphasis is on the investigation of electromagnetic field emissions which arise with the use of mobile phones and their impact on the development of brain tumors. In addition, the role of occupation-related risk factors on the development of brain tumors is investigated. A second focus of our research is on the investigation of the role of physical activity in the development of several cancer types. Physical activity is discussed as a protective factor in cancer etiology. In this context studies concerning breast cancer and colorectal carcinoma are currently considered. In cooperation with the Department „Research Topic: Infection and Cancer“ in the Division of Applied Tumor Virology at the German Cancer Research Center, the role of infections with adeno-associated viruses on the course of pregnancy and the development of the embryo is being studied. These viruses are used as vectors in tumor therapy because they have been thought of as non pathologic for humans. In cooperation with the Childrens Hospital of the University of Mainz, data of the Mainz birth registry are analyzed with regard to prenatal morphogenetic defects or malformations and possible etiological factors as well as the prevalence of oncological diseases in children with morphogenetic defects. Another research area of the Unit is quantitative risk assessment. The aim of this research activity is to quantitatively assess the relevance of certain risk factors for a set population. The results of quantitative risk assessment are an important basis for decisions in public health policy and the development of prevention strategies.

The research activities in the Division Toxicology and Cancer Risk Factors involve the identification of environment-related risk factors and studies on interactions of carcinogenic agents with acquired or inherited host factors (genetic predisposition) in human cancers. Special emphasis is given to explore molecular mechanisms by which chronic infectious/inflammatory processes induce or enhance carcinogenesis. Hereby characterization and estimation of DNA-modifications, caused by persistent oxidative stress and lipid peroxidation in cancer prone tissues and cells of human origin, should provide new insights into mechanisms and DNA alterations that act as driving force for converting a normal cell into a malignant one. An important field of research is the development of new ultrasensitive methods for the detection of DNA-damage and biomarkers for cancer susceptibility which are to be used in cancer epidemiology and intervention studies through clinical trials. Another emphasis is to build up studies in molecular epidemiology, specifically to characterize the relevance of new genetic polymorphisms, to explore further susceptibility genes of cancer, to identify risk groups in the population for prevention and screening and to further add to our understanding of gene - environment interactions. Since 1996 a project group has started to work on cancer chemopreventive agents, their mechanisms of action with future applications to human prevention trials. By selective synthesis and testing of structurally related analogues new cancer-preventive agents will be explored.

The Division Genetic Alterations in Carcinogenesis investigates carcinomas, early neoplastic lesions, and tumor cell lines for alterations in DNA sequence and changes in gene expression patterns associated with the development of cancer. Molecular profiling of tumors provides information on biological pathways and networks controlling cell life and death, and opens new avenues for novel diagnostic, chemopreventive, and therapeutic strategies. A related goal of this research program is to generate genetically engineered mouse strains with a given, precise molecular change (e.g. an inactivating point mutation in the p53 tumor suppressor gene) typical of cancer cells and known to contribute to malignant growth. These mouse models are intended to accelerate development and in vivo pre-clinical evaluation of tailored pharmaceuticals that target specific molecular alterations in human tumors. Related strains harboring human DNA sequences will also be employed to explore hypotheses on the origins of specific
genetic defects underlying human diseases, including endogenous and environmental cancer risk factors and mechanisms that elicit deleterious changes in DNA sequence.

Research in the Division of Molecular Toxicology is focused on toxicology and in drug development for tumor therapy. In toxicology the emphasis is on the analysis and the structural elucidation of DNA adducts to be used to biomonitor exposure to environmental pollutants. The current most sensitive technique is the $^{32}$P-postlabeling analysis, which however entails work with high doses of radioactivity. We have developed a method to label DNA adducts with fluorescent dyes and to analyse them by capillary electrophoresis. We have been able to detect so-called endogenous DNA adducts with this method. We are currently developing new drugs based on our concept of conjugating therapeutics to monosaccharides, to make them more water soluble and to target them to tumor. But also new structures, e.g. inhibitors of DNA repair enzymes show promising results when conjugated to monosaccharides. The specific uptake of such glycoconjugates by carrier systems leads to an enrichment of the compounds in the target organ, and reduces unwanted side effects. Complex oligosaccharides are ligands for lectins and we are trying to isolate such tumor associated lectins with synthetic oligosaccharides, to finally use them as carriers for therapeutic drugs. Another means of targeting drugs to the tumor is their covalent binding to human serum albumin. We could show that tumor cells take up albumin conjugates by endocytosis into the lysosomes, where the attached drug is liberated and kills the host cell. We have identified the proteins binding albumin on the cell surface and are currently expanding conjugation to albumin to other drugs.

In the 2002 newly established Division Molecular Genetic Epidemiology the goal has been to provide datasets for a reliable estimation in specific cancers of familial cancer risks, genetic and environmental components and modes of inheritance, and, additionally, to identify individuals in families for molecular studies of cancer. It has been used to characterize familial effects at individual cancer sites, such breast and prostate, and to assess environmental effects by comparing cancer risks among spouses. Cancer in immigrants has also been assessed. In molecular biology-mutations major effort has been directed to analysis of polymorphisms (SNPs) in cancer-related genes. In melanoma, the G1/S cell cycle checkpoint regulators have frequent abnormalities. Two linked polymorphisms in the 3'-untranslated region of the p16 gene were found to be prognostic factors. A tissue bank of bladder cancer has been used in the analysis of p53 mutations and correlated with clinical markers. Samples on esophageal cancer have been assayed for p16 mutations.