Division Clinical Epidemiology (C0500 / C020)

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The mission of the Division of Clinical Epidemiology is to conduct studies of high quality to further our understanding of the determinants of the development, prevention, early detection, diagnosis, and treatment of cancer, and to evaluate the impact of cancer control activities in these areas.

The Division of Clinical Epidemiology is the inheritor of a tradition of excellence in epidemiologic research, conducted over the last two decades. The conduct of classic epidemiology studies is the fundamental mission of the Division. The Division is well placed, within DKFZ, to collaborate with scientists in a number of Divisions in DKFZ, as well as epidemiologists, oncologists and basic scientists, within Germany, Europe, and the World as a whole.

In terms of exposures, the Division is primarily interested in genetic, nutritional, hormonal and occupational risk factors. The studies involving genetic risk factors are also designed to assess gene-environment interactions. Other aspects of aetiology, including social, economic and medical, are also included in all projects. Apart from the search for risk factors or causes in the studied groups, descriptive epidemiology, including cartographic presentation of cancer mortality, and evaluation of new statistical approaches to problems particular to observational epidemiology studies, complement the scope of activities in the Division. In Clinical Epidemiology, studies are planned relating to the evaluation of screening for several cancer sites, and discussions are being held over investigations of approaches to improve the outcome of cancer treatment.

Currently there are three major units:
- Fundamentals of Cancer Prevention
- Nutrition and Cancer
- Genetic Epidemiology
Fundamentals of Cancer Prevention (C0501)

Head: N. Becker

In cooperation with: Prof. Dr. Joshua. Muscat, Prof. Dr. Ernest L. Wynder*, American Health Foundation, New York, USA; Prof. Dr. Rainer Frentzel-Beyme, Bremer Institut für Präventionsforschung und Sozialmedizin, Bremen; Dr. Rengaswami Sankaranarayanan, Dr. Paolo Boffetta, International Agency for Research on Cancer, Lyon, France; Prof. Dr. J.F. Riemann Städtisches Krankenhaus Ludwigshafen; Prof. Dr. Maria Blettner, Faculty for Public Health, University of Bielefeld; Prof. Dr. Jürgen Berger, University of Hamburg; Prof. Dr. Volker Diehl, University of Cologne; Prof. Dr. W. Hiddemann, Dr. M. Dreyling, Klinikum Großhadern University of Munich; Prof. Dr. H.K. Müller-Hermelink, University of Würzburg; Dr. Malte Bahner, Prof. Dr. Magnus von Knebel-Doeberitz, University of Heidelberg; Numerous hospitals and practitioners as partners of the lymphoma and different screening projects

Poor progress of cancer treatment and the basic rule that prevention of disease is preferential to its treatment justify high priority to research on cancer prevention. The already now perceivable high costs of promising future molecular genetically-based treatment approaches underline the long-term relevance of cancer prevention.

The Unit Fundamentals of Cancer Prevention promotes projects which investigate or evaluate new issues or improved strategies of cancer prevention. Another focal point is secondary prevention (especially screening) because from this area the most rapid effects in terms of reduction of cancer mortality, and partially cancer incidence (including costs of treatment), can be expected.

Further activities are directed towards the identification and quantification of new risk factors for specified cancers including gene-environment interactions, especially immune response-environment (virus) interactions in order (a) to reach a mechanistic understanding, and (b) to identify possible genetically-determined high risk groups in the population. A research platform for the investigation of these factors in the field of malignant neoplasms of the hematopoietic system is being established by our participation in the European multicenter study on the etiology of lymphoma EPILYMPH (see below).

Finally, the Unit conducts the regular update of the cancer mortality data of Germany and its presentation in the Internet presentation of the dkfz. Various evaluations are performed with these data.

Epidemiologic aspects of cancer prevention in Germany

In Germany, as in other highly industrialized countries, cancer is the second most common cause of death. With approximately 210 000 individuals dying each year from malignant tumours, roughly one in four deaths in Germany can currently be attributed to cancer. Only in the past few years has there been a slow decline in the age-standardized mortality rates for cancer, even among men. This follows a long period of some decades, during which the mortality steadily increased and then persisted at a high level. The reversal, however, does not mean that the situation is no longer a cause for concern. In fact, for the most common cause of death, namely the cardiovascular diseases, a much greater decrease in mortality has been observed for many years now. If this trend continues, cancer could become the largest killer in another 15 to 20 years.

On the other hand, we have been aware since the end of the 1960s that the majority of cancers are caused by environmental influences and are thus, in principle, avoidable. In the present contribution we present (a) the fundamental arguments to support the thesis that a large proportion of cancers, and of cancer deaths, could be avoided and (b) an estimate for Germany of both the theoretical potential of primary cancer prevention and also the practically attainable potential. The estimates are based on very conservative assumptions. They yield, for the theoretical potential, values in the range 43 - 65 % and for the reduction actually obtainable in the medium term due to primary prevention, values of 18 - 31 % [1].

Quality-controlled mammography screening in Germany

Breast cancer is one of the few cancer sites for which the UICC and other institutions recommended the implementation of population-based screening, at least for a specified age-range (50 - 69 years). The recommendation was based on seven prospective randomized trials which showed a mortality reduction of up to 30 %.

Several authors proposed clinical parameters which permit the quantification and control of the performance of the entire screening process during routine operation. On this basis, the European Union released quality guidelines for the running of newly implemented screening programmes which comprise clinical, radiological and epidemiological parameters with acceptable or desirable values.

In Germany, mammography screening is not yet an official part of the health care system. However, millions of „opportunistic“ screening mammograms are carried out without quality control, paid by the health insurances. In a formal agreement between the federal boards of the associations of the general practitioners and the health insurances, so-called „model projects“ have been established within which centers for mammography screening are implemented, partially organized by, or at least in cooperation with the practitioners of the region, and following strictly the mentioned EU quality guidelines. The scope is to get experience with this system of quality-controlled screening, and to expand the system after a three-years period successively to larger areas and the entire country. The division is member of the scientific board of one of these model projects (Wiesbaden area) and supports its implementation as a consultant for epidemiological issues. Furthermore, epidemiological quality control of all model projects will be advised by the division [13].

Statistical issues of quality control in organized breast cancer screening

European guidelines for breast cancer screening recommend an integrated approach of mammography screening
with subsequent assessment and biopsy, if required, in one screening unit under permanent quality control for which target values are released. While the calculation of the respective rates (e.g., participation rate, assessment rate, biopsy rate, cancer detection rate) appears trivial, the statistical assessment of their compatibility with the target values is less obvious. This is especially true if subjects with a positive mammogram leave the screening-assessment chain prematurely, and information about further diagnostic results outside the organized screening is lacking. In this project, statistical models for the basic situation of complete information about screening and assessment outcome as well as for the mentioned situation of incomplete information have been developed, and the statistical methods for getting confidence limits, statistical tests and sample sizes needed to obtain a desired power of tests for the process parameters of interest summarized. The sample size calculations indicate that large numbers of enrolled subjects are required to obtain reasonably narrow confidence limits, and that incomplete information about outcome of diagnostic procedures among screening positives worsens the feasibility of quality control considerably. Though the methodology is specified for breast cancer screening, it should easily be transferrable to other screening issues [28].

Spiral CT scanning for the early detection of lung cancer
Every year 35 000 - 40 000 people in Germany die from lung cancer and approximately 40 000 - 45 000 people are newly diagnosed with the disease. Unfortunately, only 10 - 15% of those diagnosed with lung cancer do not die of the disease, though the 5-year-survival is dependent upon stage of diagnosis. Up to 70% of those diagnosed and confirmed to have stage Ia-disease will survive 5 years. Early detection of lung cancer theoretically should improve the outcome of the disease. Recently, evidence has occurred from uncontrolled studies in Japan and the United States that low-dose helical (spiral) computerised tomography of the lung is capable of detecting approximately four times as many small stage I lung cancers and chest x-rays, and that these appear likely to have a good prognosis. A large-scale randomised controlled screening trial of spiral CT-scanning in Germany has been proposed. The principal aim of the study is to seek new approaches that will reduce the morbidity and mortality from lung cancer. Specifically, it shall evaluate the role of annual low-dose spiral CT-scanning in the detection of and reduction in mortality from lung cancer in comparison with annual chest x-ray-screening. The trial will also provide the opportunity to evaluate other preventive prognostic and therapeutic approaches to lung cancer.

Randomized screening trial comparing once-only colonoscopy with annual faecal occult blood tests
The results of three large screening trials confirm earlier indications that a reduction of colorectal cancer mortality by up to 30 % can be achieved using the fecal occult blood test (FOBT) as the sole screening method. On the other hand, theoretical considerations based on the available knowledge about the biological development of intestinal tumours and the effectiveness of colonoscopy give rise to the conclusion that with screening by colonoscopy once in a lifetime a reduction of colorectal cancer mortality by 50 - 80 % should be achievable. However, the latter suggestion has never been proven by a randomized prospective screening trial.

In the last few years advances in imaging technology using computerised tomography or magnetic resonance imaging have raised the possibility that radiologic screening of the whole colon (virtual colonoscopy) can substitute for endoscopic colonoscopy. Currently, these approaches can not detect flat adenomas. As failure to detect flat adenomas (now avoided by high resolution colonoscopy) may have been the explanation for past failures of colonoscopy, it seems probable that once in a lifetime virtual colonoscopy would not suffice.

A study protocol has been developed which summarizes the available knowledge on FOBT and colonoscopy (high resolution and virtual) as screening methods and describes a possible approach for a randomized prospective screening trial which compares the effectiveness of FOBT and colonoscopy to reduce colorectal cancer mortality with an additional view on applicability of virtual colonoscopy as a possible further alternative.

Trial of CINtec in comparison with cervical cytology in screening for precursors of cancer of the cervix
Cervical cytology screening programs are effective in reducing the incidence and mortality from the disease. Although some benefit in reduction in mortality probably arises from the early detection of invasive cancer, reduction in incidence is due to the detection and treatment of obligate precursors of invasive cancer, especially those classified histologically as carcinoma in situ or severe dysplasia. It is unclear what contribution to this reduction in incidence is derived from the earlier detection of moderate dysplasia, as the majority of these lesions regress spontaneously, while those that progressed to CIN 3 can be readily detected and treated at that stage. However, it now seems clear that little benefit derives from the treatment of the large numbers of mild dysplasias that can be detected, especially in young women. Recently, a test specific for evidence of infection with oncogenic types of HPV has been marketed, and it has increasingly been evaluated for screening. A major difficulty with this test is that it has no ability to discriminate between transitory infections and those that are likely to be persistent, only the latter likely to be relevant to the occurrence of the cervical cancer. What is now required to overcome the disadvantages of both conventional cervical cytology and the Hybrid Capture 2-test is a test that indicates that an oncogenic HPV virus has already been integrated into the genome of the relevant cells of the host. It is believed that a new test that can be applied to both standard pap-smears and Thin Prep™ specimens which may have these desirable characteristics is CINtec. This test identifies a protein marker of persistent HPV infection, that studies to date suggest is
not expressed in normal epithelium, normal proliferating cells, inflammatory lesions, metaplastic lesion and low-grade CIN lesions not infected with high risk HPV. A study protocol has been developed to compare this new test with standard pap-smear cervical cytology.

Etiologic studies
Case-control study on the etiology of lymphoma
Lymphoma is one of the few cancer sites for which mortality is still increasing in Germany. Previous studies indicate that responsiveness of the immune system and infectious agents (viruses: EBV, HBV, HCV; helicobacter pylori) might be involved in the causation of lymphoma. These will be focal points for a case-control study which was planned during the year 1997 and started in this year. Other factors being considered in the study are exposure to pesticides, and occupational exposures to chemicals or to asbestos. A further motivation to conduct this study is that modern molecular biologically based methods of diagnosis and classification have been established and are going to be accepted internationally (REAL-classification). They allow us to investigate associations between specific exposures and specific subentities of lymphoma.

The study is being conducted in three regions of Germany (Heidelberg, Ludwigshafen and Würzburg). It is population-based and includes the age range of 18-80 years. A one to one sex- and age-matched control group is drawn from the general population. In order to carry out virological analyses and analyses of genetic polymorphisms which potentially interact with viruses, from each case and each control blood sample are drawn and frozen. Besides that, tissue material of the lymph nodes of the cases are stored to look for viral material. For this purpose, procedures are applied which allow to screen entire classes of viruses (Papilloma- and Polyomaviruses).

Asbestos exposure and malignant lymphomas
There have been a significant number of case reports on the occurrence of lymphomas in people previously exposed to asbestos. These raise the question of whether corresponding results are available from analytical epidemiological studies. In the present review of the epidemiological literature, we describe the results of the six cohort and 16 case-control studies that - according to our research - were published up to 1999 and, directly or indirectly, shed light on the above question. In summarizing the results of these studies, we have distinguished between non-Hodgkin lymphomas (NHL), chronic lymphatic leukemias (CLL) and plasmocytoma / multiple myeloma (MM). A causal relationship between asbestos exposure and the subsequent development of lymphomas cannot be derived from the available results. However, since quite a number of studies and the combined analysis indicate a (weakly) increased risk, this question should be considered directly in future epidemiological studies. Such studies should separately address the various sub-entities, employing the latest internationally agreed classification and also use the latest methods of quantifying exposure [3].

Exposure to armament wastes and leukemia: a case-control study within a cluster of AML and CML in Germany
An unusually high incidence of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) concentrated in a specific locality of a region in Germany motivated a descriptive incidence study in that region which showed a near 10-fold increased risk of CML among males but not among females [Kolb G, Becker N, Scheller S, Zugmaier G, Pralle H, Wahrenfjord J, Havermann K. Increased risk of acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML) in a County of Hesse, Germany, Soc Prev Med 1993:38:190-195]. Since a serious environmental contamination of areas in this locality with armament wastes containing toluene-derivatives has been known for a long time, the hypothesis arose that TNT production and the related severe contamination of soil and water might be responsible for the observed higher risk. We carried out a case-control study within the cluster to test this hypothesis. Overall, the results do not confirm the hypothesis. There is an indication of a relationship of an increased odds ratio with the exposure for a small group of persons who lived at a particular site in one of the two communities involved during the peak phase of TNT production during the 1940s. However, this finding is spurious and cannot explain the large majority of cases which occurred in that area in the 1980s. At the moment, no other explanation can be given for the increased risk of leukemias in that area [14].

Association of polymorphisms in $T_1$, $T_2$ cytokine genes with hay fever and atopy in a sub-sample of EPIC-Heidelberg
Lymphoma and allergies appear to have common risk factors and share genes which control immune responses that are crucial for the respective disease. In advance to the evaluation of the data and biological specimen of the case control study on the etiology of lymphoma which is planned for 2003, we established laboratory techniques for genotyping study participants for functional polymorphisms in genes relevant for immune regulation and investigated their potential role in hay fever patients.

Hay fever is determined by an interaction of environmental and genetic factors and biologically characterized by an imbalanced T helper cell $1$ ($T_1$) and $T_2$ immune response and elevated Immunoglobulin E (IgE) levels against inhalant allergens. Indications exist that polymorphisms in cytokine genes involved in the regulation of the $T_1/T_2$ balance may contribute to the allergic phenotype. We investigated whether polymorphisms in genes directly or indirectly involved in $T_1$, $T_2$ immune response are associated with hay fever and elevated IgE levels. From a sub-sample of EPIC-Heidelberg, 322 subjects with hay fever and 322 age- and sex-matched non-allergic controls were selected and genotypes determined for 15 polymorphisms in 13 genes. Plasma IgE against inhalant allergens was measured via CAPSAX (Phadiatop) test. We computed odds ratios (OR) in a two step procedure, tests on group differences of IgE-levels in dependence upon genotype and tests for trend by means of nonparametric meth-
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The cohort study “Health, Nutrition and Cancer”. A component of EPIC (European Prospective Investigation into Cancer and Nutrition)

The study “Health, Nutrition and Cancer” has been in progress since 1994 and is being run by the Division of Clinical Epidemiology of the DKFZ as part of the European long-term study EPIC (European Prospective Investigation into Cancer and nutrition). It is a multi-centre prospective cohort study and involves working groups from ten European countries and now includes a total of about 500,000 participants. Another German EPIC-centre is located in Potsdam at the German Institute for Nutrition Research (DIFE - Deutsches Institut für Ernährungsforschung). Coordination of the project is the task of the unit of Nutrition and Cancer of the International Agency for Research on Cancer (IARC), based in Lyon.[http://www.iarc.fr/epic/]

The aim of EPIC is to shed further light on the relation between diet and cancer. EPIC is trying to overcome limitations of earlier epidemiological studies in the precision and validity of traditional dietary intake measurements and limited use of biological markers.

Since EPIC is a long-term study involving several European countries with differing nutritional habits and significant variations in the incidence of specific types of cancer, it should provide an excellent set of data for evaluation. The potential usefulness is further increased by the fact that biological specimens were collected from study subjects and stored in a - for its size - unique biological databank. Thereby, the fractionated blood samples contain DNA and thus molecular investigations also form part of the scientific programme of the EPIC study.

Thus EPIC is expected to make an important contribution to a better understanding of the relation between diet and cancer. The expected results of EPIC will also enable us to give better recommendations for a healthy diet.

Actual stage of the study in Heidelberg

Recruitment

In Heidelberg the recruitment and basic assessment was completed in October 1998. This initial collection of data involved 25,544 participants from Heidelberg and the surrounding region. Of these, 53% are women and 47% men; 57% live in the town of Heidelberg and 43% in the surrounding region. A total of 24,466 (95.7%) subjects provided blood samples and these are being stored in liquid nitrogen.

For a valid measurement of dietary intake a food frequency questionnaire asking for 149 food items, portion sizes, and frequency of consumption was developed. Apart from these extensive questions about eating habits, the participants were also asked to provide information about their smoking habits, physical activity, subjective well-being, medical history and use of medications. As well as completing the questionnaire and a personal interview, the participants also gave blood samples and their blood pressure, height and weight were recorded.

First Follow-up

The future analyses of the EPIC study will depend on achieving a comprehensive record of all new cancer cases, and all deaths, together with the corresponding cause of death, within the study population. An essential element of the study is thus the subsequent further questioning of all participants at regular intervals.

The first round of follow-up questioning was completed by entering all data of the first follow-up of EPIC-Heidelberg in the data base. The participation rate was 93.5%.

Second Follow-up

New questionnaires for the second follow-up in Heidelberg were developed during the year 2000 including a questionnaire for a second measurement of diet and use of different food preparation methods [29, 72]. After a test phase the second follow-up in Heidelberg started in January 2001. This survey involves renewed questioning about medical conditions, participation in examinations for cancer screening, smoking habits, physical activity, intake of drugs, hormone preparations and food supplements. By the end of the year 2002 about 15 000 questionnaires had been mailed. So far a response rate of over 90% can be anticipated.

Verification of cancer cases

According to the general conditions in the study region active follow-up to obtain end-point data is necessary. To date all self-reported incident cancer cases are verified by comparing them with pathology reports and hospital records. They are then coded according to the coding list for the International Classification of Diseases (ICD-O2) issued by the World Health Organisation (WHO).

In order to integrate increasingly the data of the Cancer registry Baden-Württemberg attempts were made to implement a new record linkage system. For this purpose, a procedure has been developed for performing an anonymous linkage of the EPIC data with the data of the Cancer Registry. After a pilot project on the feasibility of the linkage the program was evaluated on the EPIC data, record linkages are performed regularly. So far the active follow-up can not be replaced by passive follow-up through record linkage with the cancer registry, but in the long-term it may be possible.
Simultaneously, our data about new cancer cases among the Heidelberg study participants will be passed on to the Cancer Registry, thus helping to make this more complete.

Results
Nutritional epidemiology contributes to the scientific evidence on which prevention strategies for chronic diseases are based [82, 90, 91]. Therefore it is important to monitor dietary and lifestyle changes over time. EPIC Heidelberg as well as the Danish EPIC group required completion of a Food Frequency Questionnaire (FFQ) in the second follow up. Analyses to explore changes in dietary habit between recruitment and follow-up point of measurement were performed.

The scientific activities comprised pilot studies on biomarkers using biological specimens to explore the influence of various genetic polymorphisms on the risk of disease. Some projects were successfully completed, such as an analysis of the modulatory effect of candidate genes on obesity [68]. Associations between single nucleotide polymorphisms (SNP) in the fatty acid oxidation pathway, inflammation parameters and hay fever were investigated. Other projects were to explore the relation between genetic changes and risk of cancer, such as plasma oxysterols as markers of lung cancer. Based on the calculation of specific nutrients such as flavonoids [70], phenolic acids, and conjugated linoleic acids the influence on the selected cancer sites was evaluated.

Another research interest was the evaluation of dietary supplements measured at the first follow-up. After the use of supplements and its determinants have been quantified, their impact on disease is the focus of interest. Another project investigated the body composition, dietary and smoking habits, according to alcohol intake. In order to describe the effect of dietary patterns on colorectal cancer risk a score considering the main food groups was developed. Moreover, results on the influence of dietary intake of fatty acids and antioxidants on the adult onset of hay fever were evaluated.

Some pilot-studies have been initiated such as:
- Study on the influence of dietary fatty acid, vegetable and vitamin intake on etheno-DNA-adducts [9]
- Study on the relationship between cholesterol oxidation and lung cancer [53]
- Study on lipid oxidation and breast cancer risk
- Study on dietary pattern of patients with Non Hodgkin's Lymphoma

On the national level, the collaboration with the EPIC centre in Potsdam led to comparative analyses of the nutrient intake and lifestyle factors of both cohorts. The investigations focused on macronutrient, vitamin, and mineral intake [31, 55] as well as on fatty acids, carbohydrates and dietary fibre intake. The smoking habits in both centres were analysed [73]. Analyses on changes of smoking habits during the past forty years were conducted.

Based on the preliminary work of EPIC-Potsdam on recipes derived from the 24 hour recall data, in co-operation programs for the calculation of nutrient and food groups were elaborated. This may provide better estimates of micronutrient intake.

Estimates of risks associated with the various exposure factors will become possible when a sufficient number of new cases of a particular cancer have been recorded. For Germany, it is expected that, together with DIFE in Potsdam, we will be able to present such estimates in approximately 2004.

In 2001 the European Conference on Nutrition and Cancer was held in Lyon. Results of this meeting were summarized in the IRAC Scientific Publication No 156. Scientists from EPIC Heidelberg contributed to summaries on lung cancer [82, 89, 92], dietary patterns [90, 91, 92, 95] and plasma concentrations of fatty acids [96].

Descriptive analyses on European level regarding relevant exposure factors such as diet, anthropometry and physical activity were performed and prepared for publication as Supplement of the Public Health Nutrition.

The nutritionist of the Heidelberg EPIC-group had a leadership role within the EPIC working group on dietary patterns for the following areas:
- dietary fat and oil intake [91]
- dietary meat intake [90]
- food preparation methods applied to meat and fish [95]

Analyses for the pooled data of all EPIC-countries have already begun for food group intake and the most common cancer types (breast, lung, colorectum and prostate). For colorectal cancer, the activities were focused mainly on the association between dietary fibre consumption and risk. The results on fibre intake and colorectal cancer were submitted for publication. In the lung cancer working group, which is co-ordinated by EPIC Heidelberg, results on associations of fruit and vegetable intake with incident lung cancer [92] were evaluated and prepared for publication. Subsequently, up-dated data were used in further analyses regarding special subgroups. The on going cooperation projects EUR-GAST and GEN-AIR were supported with material and data.

Moreover, we are actively supporting the development of a Standardised European Food Composition Table.

Unit of Genetic Epidemiology (C0505)

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In cooperation with: Prof. Dr. Helmut Bartsch, Prof. Dr. Jürgen Debus, Dr. Angela Risch, Dr. Peter Schmezer, Prof. Dr. Heinz Thielmann, all DKFZ; Prof. Dr. Heiko Becker, Institut für Tropenmedizin, Universität Heidelberg; Prof. Dr. Gunther Bastert, Prof. Dr. Dietrich. von Fournier Universitäts-Frauenklinik Heidelberg; Prof. Dr. Ludwig Braendle, Dr. Dieter Flesch-Jayas, UKE Hamburg; Prof. Dr. Ingo Runnebaum, Universitäts-Frauenklinik Freiburg; PD Dr. Marion Kiechle, Universität München; Prof. Dr. Rolf. Kreienberg, Dr. Shan Wang-Gohrke, Universitäts-Frauenklinik Ulm; Prof. Dr. Heidi Hahn, Universität Göttingen; Prof. H.-E. Wichmann GSF, München; Prof. Dr. Thomas Winkler, Universität Bonn; Prof. Dr. Christine Ambrosone, Roswell Park Cancer Institute, Buffalo, USA; Prof. Dr. Duncan Thomas, University of Southern California, Los Angeles, USA; Dr. Alison Dunning, Prof. Douglas Easton, Prof. Bruce Ponder, Medical Research Council, University of California, Los Angeles, USA; Dr. Alison Dunning, Prof. Douglas Easton, Prof. Bruce Ponder, Medical Research Council, University of California, Los Angeles, USA.
The research activities of this unit aim at the elucidation and quantification of the joint effects of genes and environmental factors in the etiology of breast cancer in the general population. In this endeavour, modern molecular genetic methods will be incorporated in the studies in order to employ biomarkers for the quantitative assessment of exposure and the characterisation of genetic susceptibility.

Inherited susceptibility can be due both to genes which confer a high degree of risk (major genes) and those which have a smaller effect on disease risk (polygenes). Population-based genetic epidemiologic studies of breast cancer and of ovarian cancer have been carried out to provide the basis for identifying relevant genetic variants conferring low to moderate disease risk and studying their interaction with environmental factors, such as between polymorphisms in metabolizing enzymes and passive or active exposure to tobacco smoke. Larger population-based studies in combination with high throughput technologies are planned to allow efficient identification of association between allelic variability in candidate genes, exposures, such as hormone replacement therapy, and cancer risk. To better understand the risks conferred by the highly penetrant BRCA1/2 genes, collaborative studies on familial breast and ovarian cancer with several European centres will be used both to further develop risk assessment of familial breast and ovarian cancer and to identify modifiers of risk. For genetic mapping of further predisposing genes for breast and colorectal cancer, we will exploit the stronger linkage disequilibrium generated by genetic drift and/or founder effect in isolated populations and employ novel methods of “haplotype sharing analysis” to identify disease associated haplotypes. Genetic susceptibility can influence the extent of clinical radiation reaction and the success of radiotherapy. The impact of constitutional radiosensitivity to ionizing radiation needs to be quantified in prospective studies in which simultaneously the usefulness of bioassays to predict constitutional radiosensitivity can be examined.

Genetic-epidemiologic studies of breast cancer

The long-term objectives are the study and characterization of genes involved in the etiology of breast cancer and the investigation of gene-environment interactions using data from two subprojects: (i) family study of hereditary breast and ovarian cancer and (ii) population based case-control family study of breast cancer in women under 51 years of age.

Families with at least 3 cases of breast or ovarian cancer recruited from all over the country in Germany were initially studied to establish the involvement of the BRCA1 and BRCA2 loci. Further linkage and association studies performed in collaboration with the Breast Cancer Linkage Consortium have excluded strong linkage to loci at 8p and 13q21 and provided evidence of low-penetrance susceptibility due to a CHEK2 functional variant. Modification of the penetrance of BRCA1 and BRCA2 by life-style/environmental factors will be studied in collaboration with European centers and the International BRCA1/2 Carrier Cohort Study.

Newly diagnosed breast cancer patients up to the age of 50 were recruited 1992-1995 from two study regions in Germany, “Rhein-Neckar-Odenwald” and “Freiburg-Breisgau-Emmendingen-Ortenau”, including about 2.2 million inhabitants. Two sets of controls were enrolled for each case: a) two unaffected age-matched women from the same study region and b) an unaffected sister. Data on known and suspected exogenous risk factors were collected and biological material for molecular genetic analyses.

The results of case-control analysis of the questionnaires show that the length of breastfeeding reduces the risk of breast cancer significantly, independently from the protective effect aligned with the number of given births. High daily alcohol consumption was associated with an elevated breast cancer risk, whereas a low or moderate consumption did not increase the risk. Analysis of the food frequency questionnaires revealed a reduced risk of breast cancer with increasing vegetable intake, and an increased risk with a high consumption of red meat (beef and pork). The prevalence of BRCA1/2 mutations was determined by mutation screening in a small series of unselected young patients under 40 years old. Association studies have been carried out, in order to identify risk-modifying genes (e.g. in the metabolism of hormones such as the progesterone-receptor-gene, and DNA repair such as BRCA2) and assess their role in breast cancer aetiology. Epidemiologic data and blood samples from this study are continually being used for further studies to identify genetic susceptibility factors for breast cancer and gene-environmental interactions in collaboration with national and international partners.

Genetic-epidemiologic study of ovarian cancer

Newly diagnosed ovarian cancer patients up to the age of 75 were recruited from two study regions “Rhein-Neckar-Odenwald” and “Freiburg-Breisgau-Emmendingen-Ortenau” from 1993 to 1995. Two unaffected age-matched controls from the same study region were enrolled for each case. Data on known and suspected exogenous risk factors and blood samples for molecular genetic analysis were collected. The results of the case-control analysis of the questionnaire data clearly showed that the intake of oral contraceptives offered a protective effect. This protective effect was also observed for low-dose oral contraceptives.

Mutation screenings for germ-line BRCA1 mutations have been carried out in patients with a family history of breast or ovarian cancer and in patients diagnosed less than 45 years of age. Association studies are being planned to identify genetic susceptibility resulting from genetically determined variance in the metabolism of hormones.
Genetic predisposition as risk indicator for breast cancer after exposure to active and passive smoking

Different genotypes respond differently to exposure to recognized environmental factors. The effect of genetic polymorphism of relevant metabolizing enzymes, such as N-acetyl transferase 1 and 2 (NAT1, NAT2), glutathione transferase T1 (GSTT1) and cytochrom-P450-enzymes, on the risk of breast cancer associated with active and passive smoking was studied. Subjects of the completed case-control study of breast cancer were recontacted for additional detailed information on exposure to cigarette smoke (active and passive). Genotyping was carried out by the Division of Toxicology and Cancer Risk Factors. Compared to neither active nor passive smokers, ever active smokers had a 31% increase in risk of breast cancer. Amongst never active smokers, passive exposure to tobacco smoke was associated with a significant increase in risk of 59%. Relative risk of breast cancer was increased for carriers of a NAT*10 allele and of a CYP2A6*2 allele, with statistical significance only for the NAT*10 allele. Main effects of other examined genetic variants (GSTM1, GSTT1, CYP1A1, NAT2) on breast cancer risk were not found. However, some of these genetic variants had a modifying effect on the association between breast cancer risk and tobacco exposure. For example, when comparing exposed women to never actively or passively exposed women, breast cancer risk was differential for NAT2 status. Slow acetylators had a higher risk for active exposure, whereas fast acetylators had an increased risk when passively exposed. Further analysis will focus on gene to gene interactions and gene-environmental interactions.

Hormone replacement therapy and the risk of postmenopausal breast cancer - The MARIE Study

With increasing frequency, hormone replacement therapy (HRT) is being prescribed for a range of health reasons, from the alleviation of climacteric conditions to improved quality of life and the prevention of cardiovascular diseases and osteoporosis. Clarification, therefore, of the possible effects of HRT on breast cancer risk in Germany is of vital importance. Goals of the population-based case-control study are to assess how lifestyle factors, such as pregnancies, smoking, alcohol, nutrition, physical activity, and HRT influence the development of breast cancer, to quantify these modifying factors by histological types, to measure the effects of various forms, duration, and timing of HRT on breast cancer risk, and to determine the role of genetically-based differences in the regulation and metabolism of hormones.

Data collection began on August 1st 2002 in the Rhein-Neckar/Karlsruhe/Heilbronn study region. With the cooperation of regional hospitals and clinics, women with primary breast cancer, between the ages of 50 and 74 are being contacted and interviewed using a standardized questionnaire. A photo list of hormone packages will be presented to study participants to improve the quality of data collected on HRT use. Two control persons (without breast cancer) per case from the same study area will also be recruited. This study, funded by the Deutsche Krebshilfe, is being conducted simultaneously in Hamburg and aims to include a total of 3500 cases and 7000 controls.

Case-only study on the interaction of diet and genetic predisposition in the occurrence of breast cancer in young women

A case-only design provides more power to detect gene-environmental (GxE) interaction effects but does not permit estimation of main effects. This study aims to determine whether effect of known risk factors on breast cancer risk, in particular dietary and other life-style factors, is modified by genetic predisposition (GxE) and provide the basis, in the long term, to develop preventive strategies for genetic counselling and for dietary intervention trials.

Breast cancer patients under 40 years of age at the time of diagnosis from 1998 to 2002 and resident in the Rhein-Neckar-Region, the Ortenau county and the State of Rhineland-Palatinate will be recruited and epidemiologic data collected using self administered questionnaires. The genetic risk will initially be estimated based on complete family history information. The study is funded by the European Union and will be carried out in seven countries (Germany, France, Scotland, Latvia, Slovenia, Italy and Israel) with the aim of recruiting several thousands of early onset breast cancer patients.

Genetic mapping of breast cancer susceptibility genes using „haplotype sharing analysis“ in isolated populations

Haplotype-based association (linkage disequilibrium) methods have been proposed for mapping genes involved in complex traits in populations where genetic heterogeneity is reduced due to founder effect, bottleneck and genetic drift. Haplotypes capture the local linkage disequilibrium information and are therefore more informative than single markers. Haplotype sharing analysis is a statistical tool to identify regions on the genome which are associated with specific diseases. This method will be employed to map breast and colorectal cancer susceptibility genes in the population of the Oberlausitz in Saxony. The population of this region includes Sorbs, Oberlausitzer and Schlesier whereby the Sorbs, due to their history, are most likely to fulfill the criteria of an isolated population. Breast and colorectal cancer patients diagnosed 1992-2001 as well as their parents/nuclear family (required for haplotyping) have been recruited: blood samples and epidemiologic data collected using a questionnaire. A genome screen is planned in cooperation with the Gene Mapping Center in Berlin and the haplotype sharing statistic will be used to evaluate shared segments for disease associated haplotypes.

Available statistical methodology for haplotype sharing analysis will be initially established and examined in the context of complex diseases. Further development of the statistical methods will be conducted to more efficiently determine haplotype sharing and take covariates into consideration based on Mantel statistics.

The impact of constitutional radiosensitivity on the estimation of the individual health hazard caused by occupational
exposure to ionizing radiation under given exposure condi-
tions.

Intrinsic factors of individual radiosensitivity are consid-
ered to influence the variability of side effects observed af-
after exposure to ionizing radiation. The two prospective
studies performed in this research area aim to (1) estimate
the proportion of radiosensitive persons in the population,
(2) establish in vitro assays to identify these individuals,
(3) identify underlying genetic patterns responsible for ra-
diosensitivity, and (4) identify other factors modifying the
severity of symptoms.

The studies are implemented in radiotherapy patients
(breast cancer, prostate cancer and leukemia/lymphoma)
using radiotherapy side effects as indicator for radiosensi-
tivity. Epidemiologic data are collected using question-
naires as well as patients records and a blood sample for
the laboratory analysis.

In the study population of 478 breast cancer patients, 84
experienced a skin reaction of degree 2c or 3 (a moist
desquamation or discontinued radiation due to adverse
side effects). A higher age was associated with a lower risk
of developing skin reactions of degree 2c/3. Patients with
a higher BMI showed an elevated risk for these skin reac-
tions. The DNA repair-capability determined for each indi-
vidual via alkaline Comet-Assay (cellular test) was not as-
associated with the acute adverse side effects.

Inherited polymorphisms in genes that affect capabilities to
protect cells from reactive oxidant damage and in those
that repair damaged DNA will affect outcomes among
women treated for breast cancer. In a follow-up study, we
will evaluate the role that genetic variability may play in
disease-free survival, as well as treatment-related toxicity
after radiation therapy. Specifically, we shall investigate
whether women with genetic variants affording less protec-
tion from DNA damage or decreased repair of treatment-
generated damage will have more severe skin reactions,
but better response to treatment for breast cancer, with a
lower hazard of recurrence.

Other epidemiologic studies

(1) Nested case-control study of a cohort of man-
made mineral fiber workers

In cooperation with P. Boffetta, IARC, Lyon, France and other Eu-
ropean collaborators

Within the international cohort study coordinated by the
IARC on man-made mineral fiber workers, a nested case-
control study was carried out to assess lung cancer risk
associated with fibre exposure, taking into account pos-
sible confounders such as smoking, alcohol and other oc-
cupational factors. Exposure assessment was carried out
incorporating both information from next-of-kin and from
an expert panel of foremen and engineers of the plant. Af-
ter adjusting for smoking, no evidence remained of a car-
cinogenic effect of mineral and slag wool exposure.

(2) Extension of follow-up of the cohort study of
German vegetarians (21 years mortality)

The lifestyle characteristics of a cohort of 1904 Germans
adhering mainly to a vegetarian diet have been examined in
relation to their mortality since 1978. The level of physi-
cal activity, the duration of vegetarianism and the vegetari-
ian status (strict versus moderate) were found to be deter-
minants of total mortality, cancer mortality and/or mortality
from cardiovascular diseases. A collaborative analysis of
five prospective cohort studies comparing the mortality of
vegetarians to non-vegetarians identified a lower risk of
dying from ischaemic heart disease. A significantly re-
duced mortality of the cohort persisted in the extended fol-
low-up of the German cohort to the end of 1999. Based on
larger number of deaths analyses will be performed to
identify determinants of the mortality from some specific
cancer sites.

Future

The unit plans to conduct further large-scale population-
based epidemiologic studies with standardized data and
blood sample collection, including breast and colorectal
cancer. These studies will provide the basis for association
studies to identify multiple genetic susceptibility factors,
gene-gene interactions and gene-environmental interac-
tions for breast cancer and colorectal cancer associated
with exposure to hormones and chemical carcinogens.

Particular patient populations, such as early onset breast
cancer, will be targeted for the identification of modifying
factors of genetic susceptibility in efficient case-only stud-
ies. Collaboration on relevant studies will be sought within
DKFZ and with national and international partners to make
full use of the resources.

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