Report

The UICC Familial Cancer and Prevention Project 1991-2003

Taking the **family history** of cancer patients is a low technology approach which can be applied all over the world. It is a tool to identify high risk persons and families and to down-stage disease by targeted preventive and therapeutic approaches. Families with cancer members are motivated by this approach.

The operational definition of **familial cancer** is: two or more affected first degree relatives. This definition applies to 10% to 30% of all cancer patients.

The UICC Familial Cancer and Prevention Project was launched in 1991 by Dr. K. Aoki, Dr. M.M. Burger and Dr. W. Weber in Lugano, Switzerland. It promoted familial cancer control worldwide until 2003. The **activities** were:

1. Establishment of nodal points in Australia (D.J.B. St. John, R. Scott), Egypt (R. Bedwani), Japan (J. Utsunomiya), Poland (J. Lubinski), USA (J.J. Mulvihill) and Switzerland (M.M. Burger, W. Weber).
2. Establishment of the Familial Cancer Database – FaCD (www.facd.info).
3. A simple family history questionnaire has been developed for comparisons of family cancer data in different countries.
4. Ten project meetings were held in Brazil, India, Italy, Japan 2x, USA 2x and Switzerland 3x.
5. Four educational seminars took place (in Belgium, Israel and Switzerland 2x).
6. The first international symposium was held in Japan.
7. An international research conference took place in Switzerland.
8. An international symposium on familial cancer and prevention in 1997 in Kobe, Japan.
9. Combined Project and Oncology Conferences in 1999 in Karachi, Pakistan, in Alexandria, Egypt, and in 2001 in Beijing, China.
10. Initiation of family studies in Poland and neighbouring countries.
11. Pilot study: Cancer in first-degree relatives of Latin American women with cervical cancer.
12. International conference on familial cancer, 5-7 June 2003, Oklahoma City, USA.

The ending UICC project is transformed into **an international network with minimal infrastructure:** Familial Cancer Prevention, Detection and Care Network (FCPDCN). The existing nodal points continue to work as framework of an informal and open communication system: Asia: J. Utsunomiya (utunomiy@junshin.or.jp), Australia: R. Scott (rscott@doh.health.nsw.gov.au), Europe + Africa: J. Lubinski (lubinski@pam.szczecin.pl) and W. Weber (cancer@bluewin.ch), USA: J.J. Mulvihill (john-mulvihill@ouhsc.edu), Central America: M. Garcés (mgarces@url.edu.gt). The funds needed will have to be raised. The main **objective** is to promote the use of the family history for cancer control by generating and sharing information. The main **instruments** are: events, pilot studies and publications in Hereditary Cancer in Clinical Practice (editor@hccp-uicc.com or www.hccp-uicc.com). The readers are invited to contact the nodal points of their choice and to present their ideas and suggestions.

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UICC Familial Cancer Project Meeting
Leuenberg near Basel, September 13, 1995

(Program: see Addendum 1)

Ten UICC Programs are presented and discussed by Dr. M.M.Burger. The Familial Cancer Project is one of the seven projects in the Program for Epidemiology and Prevention (Chairman: Dr. S.Tominaga).
Another special project is Molecular Epidemiology (Chairman: Dr.Kitagawa,). Dr.M.M.Burger encourages to bundle the activities of a.) Detection and Diagnosis b.) Familial Cancer c.) Tumor Biology.
Dr. W.Weber, coordinator of the UICC Familial Cancer Project, presents the planned activities (see Addendum 2). The project structure will consist in a first phase in 3 nodal points, one in Japan, one in Switzerland and one in the USA. The minimal requirements for a nodal point are: A computer connected to GLOBALINK and INTERNET plus a parttime secretary. Dr. W.Weber is installing a nodal point for Europe and Africa in Basel / Bern. An international advisory board has been established. Dr. G.N.Stemmermann,(Cincinnati), will contact Dr. J.J.Mulvihill, (Pittsburgh), for a nodal point in USA. Dr. W.Weber will explore possibilities of support by the American Cancer Society . The first international project activities will be to start a newsletter and to exchange anonymized family data and biological specimens.
Dr. Shozo Baba gave a most informative presentation on diagnosis, treatment and follow-up of FAP and HNPCC. The audience was impressed of the efforts made in Japan. 300 institutions follow 5000 colorectal carcinomas per year. 700 FAP families, 300 HNPCC families (Amsterdam criteria) and 4000 HNPCC families (Japan criteria) are under surveillance out of a series of 73785 colorectal cancer patients. Dr. Shozo Baba has organized and presided the International Symposium on Hereditary Colorectal Cancer in Hamamatsu on July 8, 1995; supported by J.Soc. for Cancer of the Colon and Rectum and J.Soc. of Coloproctology. Dr. Baba has himself treated 74 FAP patients in 40 families. Germ line mutations were identified in 11 of 30 persons. He is also managing 20 HNPCC families including the largest family in Japan. Germ line mutations of hMLH-1 and hMSH-2 are identified in mouthwash samples in collaboration with Prof. Y.Nakamura.

The Hawaii Family History Questionnaire
(Addenda 3+4).

Dr. G.N.Stemmermann has developed a simple code sheet for obtaining data on tumor occurence in first-degree relatives. Anamnestic data are compared to registry data. Data of pilot studies with this simple questionnaire were presented from Hawaii by Dr. G.N.Stemmermann , from Trieste by Dr. D.Brunetti, from Basel by Dr. P.Mussio and from Liestal by Dr. W.Weber.

Hawaii: 40 families studied. The time required for interviewing and computer search in the registry is 1 hour (30 minutes each).
It is difficult to get accurate birth dates; anamnestic diagnoses can successfully be rectified or falsified in corresponding population based cancer registries; a nurse gets more information as a secretary; 2 childhood tumors (malignant lymphomas) were observed - both were unknown to the parents and found through the registry only.

Trieste: 193 families studied. Sensitivity: 85 %, specificity 97 % and overall accuracy 95 %. Considering the 83 true positive cases, probands identified correctly the primary site of 71 cases (86 %) and recalled exactly the age at diagnosis of 79 (95 %). These results suggest that studies on familial cancer based on anamnestic data reported by probands are sufficiently accurate.

Basel: 64 families studied. Sensitivity: 74 %, specificity 97 %, true positive 74 %, false positive 26 %. The intraclass correlation coefficient is 0,69 which represent a fair to good agreement beyond chance.

Liestal: 43 families studied. 9 tumors were identified only by medical record review. They occured at the following localisations: skin (4x), pancreas, urinary bladder, leucemia, prostate and colon.

Conclusions: Future use of the Hawaii Family History Questionnaire is limited to places with population based registries. In addition the legal and ethical guidelines of a country will have to be observed. Date and cause of death and permission to review medical records of the person interviewed might be added to the questionnaire. Doctors have to be educated to elicit a family history and legal protection of the families is warranted.

General conclusion
Dr. M.M.Burger, Treasurer of UICC, urges the establishment of 3 nodal points within a year with the tasks clearly defined and with a program for the subsequent 3 years.

Basel/Bern 18.9.1995

Wednesday afternoon / evening, September 13, 1995

UICC Familial Cancer Project

The Family History

Baba Shozo, Hamamatsu	Honorary President
Burger Max M., UICC, Basel	Chairperson
Stemmermann GN, Cincinnati	Chairperson
Brunetti Davide, Trieste	Rapporteur
Thelma BK, New Delhi	Editing

Baba Shozo, Hamamatsu	Activities in Japan
Burger Max M., Basel	UICC Programmes
Weber Walter, Basel	The Familial Cancer Project

The Hawaii Family History Questionnaire

Stemmermann GN, Cincinnati Brunetti Davide, Trieste Mussio Peter, Basel Weber Walter, Basel	Pilot Studies

Thelma B.K., New Delhi:	Comments from India

General Discussion

Conclusions

Taking a Family History	Contributions by the participants
Techniques, Experiences, Difficulties , Proposals	

Addendum 2

UICC Familial Cancer Project

Goal

Use of the family history for cancer control

Activities Planned

1. **Collect and exchange family data**
2. **Newsletter (exchange of data, opinions , biological material etc.)**
3. **Coordination and promotion of family studies**
4. **Study existing data bases**
5. **Collect and exchange biological material**
6. **Expert meetings**

Nodal Points

1. **Japan for Asia, Australia and Oceania**
2. **Switzerland for Europe and Africa**
3. **USA for the Americas**

Addendum 3

LY CODE: 11=FATHER, 12=MOTHER, 21=BROTHER, 22=SISTER, 31=SON, 32=DAUGHTER

	FIRST NAME, MIDDLE	CARCINOMAS		
			(ICD-9)	AGE (YR)
BIRTHDATE				
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
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			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)
			(ICD-9)	AGE (YR)

PATIENT'S NAME: _____ _____ _____ [_____]
FAMILY NAME FIRST NAME MIDDLE NAME MARRIED NAME

BIRTHDATE:

CARCINOMA (ICD-9)_____ DATE DIAGNOSIS

PRIOR CANCERS (ICD-9)_____ ;_____

FAMILY HISTORY

Addendum 4

FAMILY HISTORY CODE SHEET

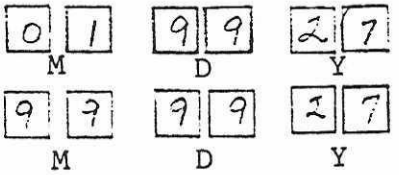
Directions for Use

1. The interviewer should enter the names and cancer diagnoses in longhand.

2. The ICD-9 codes will be entered by the Tumor Registry code clerk.

3. If the family members are too numerous for one (1) code sheet, add more code sheets, as necessary; but make certain that the information on the index case (last 3 lines on code sheet) is repeated on supplemental code sheets.

4. In the case of birthdate, enter 9s for unknown information, thus:



month & year known, birthday unknown

month & birthday unknown

5. The age listed for each cancer should indicate the <u>age at diagnosis</u>. If this is unknown, enter 9 9

6. The completed code sheet should be made part of the patient's Tumor Registry record.

7. The treating physician should be alerted if a substantial family risk is uncovered by this interview.

International Union Against Cancer
Union Internationale Contre le Cancer

Epidemiology and Prevention Programme
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Familial Cancer and Prevention Project Meeting in Rio de Janeiro, Brazil Tuesday, August 25, 1998, 1 pm - 6 pm Hotel Inter-Continental

Report

1. **Welcome**
W. Weber, coordinator of the UICC Familial Cancer and Prevention Project, welcomes the invited experts (Encl. 1)
He presents a report on the achievements of the latest 4 year period 1994-1998 (Encl. 2)
Every activity of the FCPP must result in publications.

2. **The UICC Epidemiology and Prevention Programme**
S. Tominaga, chairman of the programme, presents the six projects, and he points to the UICC Statement on Diet, Nutrition and Cancer Control (Encl. 3)
S. Tominaga congratulates W. Weber for being elected into the UICC council on August 22, 1998.

3. **Familial Cancer in Latin America**
Cervical cancer is the most frequent malignancy of women in Latin America. Cervical cancer control programs are started in several countries.
W. Weber would like to start a new subproject on familial cervical cancer.
This is supported by Latin America and Japan. Criticisms are expressed:
   a) cervical cancer is rare in many countries and intercountry comparisons will therefore be difficult.
   b) one should start with a cancer where familiality is high like familial breast and colorectal cancer.

Therefore these two localisations might also be included in a study in Latin America.

4. **Japan Society of Familial Tumours and Prevention (JSFTP)**
S. Tominaga and S. Baba convey greetings and best wishes from Dr. J. Utsunomiya, the president of the Japan Society of Familial Tumors and Prevention, which was founded in 1994.
Dr. Utsunomiya is having a training course for familial cancer counselors with 30 faculty members. In January 1998 he has successfully held a Train the Trainer Seminar for cancer genetics with cooperation between the Japanese Society of Medical Genetics and the JSFTP.
Dr. Utsunomiya is now operating a Familial Tumor Center and an Oncology Home Care Program on Sado island next to Kobe.

5. Mutation Atlas of Genes for Inherited Cancer (MAGIC): an IARC initiative

G. Lenoir presents MAGIC, an IARC project started in 1997 by Dr. D. Goldgar and himself. The role of specific high-risk mutations in most parts of the world remains almost completely unexplored.
A first pilot study is addressing breast cancer (BRCA 1+2). The cancer registries have been contacted. Laboratory people are trained in Lyon to identify mutations. IARC has the goals to contribute at the world level to the understanding of cancer and to do technology transfer. Counseling has to be build up in parallel to mutation testing. A corresponding genetic counseling network could be developed by UICC in collaboration with IARC.

6. Familial Cancer in Poland

J. Lubinski reports on the national efforts of the Hereditary Cancer Center in Szczecin. Questionnaires are sent throughout the country and 500 cancer families have been identified up to now. A central data base has been started in 1998. The following mutations have been detected: 7 BRCA1, 5 BRCA2, 5 FAP, 5 hMLH1, 3 h MSH2, 16 VHL, 8 RET and 6 RB-1.
Families are counseled and preventive measures are taken. Lives have been saved. The economical justification is easily calculable.
J. Lubinski will prepare a proposal on a new subproject based on activities in Poland. Its major goal will be medical practice. J. Lenoir points to the important fact of the two well defined situations FAP (many polyps in the colorectum) and MEN2 (2 cases of medullary thyroid cancer) where state of the art medical management can immediately be realized.

7. Draft „Study of Ethnic Differences in the Heritable Fraction of Childhood Cancer"

D. Brunetti presents a first draft of this important new subproject (Encl. 4).
So far only two population - based studies have been done:
1. S. Narod and G. Lenoir Br. J. Ca. 1991 and
2. D. Brunetti Int. J. Ca. 1997.
The first phase of this third study will be a pilot study with a few participants from different continents. The data management will be started in Trieste with the advice of Dr. L. Tomatis. It is suggested to concentrate on certain tumors. The following topics could be of interest: Increased frequency of Hodgkin's disease in Latin America, enormous ethnical variation of Ewing's sarcoma, look at populations with high consanguinity (recessive traits).

8. UICC Family History Questionnaire

The Questionnaire (Encl. 5) has been validated and is offered for free to the human community for taking family histories in cancer patients (Mussio P. et al. Anticancer Research 18: 2811-2814, 1998). It is important to enter all first degree relatives into the questionnaire.
The questionnaire subproject is terminated.

9. Familial Cancer and Prevention Journal

There is a need for a Journal for people working with cancer patients and their families. The content of such a journal could be:

1. Pedigrees
2. Newly detected single mutations
3. Family history data
4. Linkage mapping
5. Guidelines
6. Practical aspects
7. Ethical, legal, economic and psychosocial issues
8. Counseling

The Journal should be partly paper partly electronic.
The following persons would be interested in participating in the project and editorial board: Ruben Israel, Jan Lubinski and Rodney Scott. The project nodal points should also participate.

10. Newsletter

There is a definite need for the newsletter to go on.

11. Directory of Family Tumor Study Groups

W. Weber has written a letter to Dr. P. Kleihues, asking if IARC might be interested in writing a directory.

12. Events

see Encl. 6

13. Miscellaneous

- Future activities of LCPG and ICG-HNPCC should be coordinated and crosspromated with the UICC FCPP.
  LCPG is considering UICC membership.
- S. Baba explains the importance of clarifying how environmental factors affect familial cancer by looking at the geographical distribution of second primaries in familial cancer syndromes.
- R. Bedwani did a pilot study with the UICC Family History Questionnaire in Alexandria. A positive family history was elicited in 12% of 400 women with breast cancer.

07.09.1998, Walter Weber, M.D.

- Encl. 1-6

UICC Familial Cancer & Prevention Project and VII International Oncology Conference March 10-11, 1999 Pearl Continental Hotel, Karachi, Pakistan

This interdisciplinary oncology conference was attended by approximately 250 doctors from 20 countries. Dr. Imtiaz A. Malik, Director National Cancer Institute in Karachi has organized it with the help of Dr. Shakeel Amanullah, Karachi, Ms Regula Schneider, Bern and myself.

The three most common cancers in Pakistani men are lung cancer, squamous cell head and neck cancer and non-Hodgkin's lymphoma (NHL). The three most common cancers in Pakistani women are: breast cancer, ovarian cancer and gall bladder cancer. 40 % of world incident cancers occur in Asia (3,8 million). Asia accounts for more than three fourths of world total naso-pharyngeal, oesophageal and liver cancers, for more than half the oral cavity, stomach and uterine cervical cancers and for a third of the world total of colo-rectal, lung and breast cancer cases. There is considerable regional variation. The survival figures correspond to those observed in United States three decades ago.

Familial cancer clustering is observed world-wide. All sites show an excess of cancers of the same site among relatives. Familial associations are useful in generating hypotheses about specific genetic and environmental factors that can be tested in genetic-epidemiologic studies. The high prevalence of consanguineous marriages and large families in Pakistan calls for studies to identify recessively inherited predispositions which may contribute to familial clustering of malignant lymphomas.

Genetic testing of persons at risk has two main purposes: the identification of individuals who are likely to develop early onset disease and the determination of the molecular basis of the disease in question. The costs of genetic testing will decrease and genetic screening will become a cost effective method of reducing overall medical costs for patients and their relatives.

Lung cancer clusters in families. Significant risk determinants are age, sex, tabacco, smoking, occupational and industrial exposures, a positive familiy history and the ability to metabolize debrisoquine.

Squamous cell head and neck cancer is very frequent in Pakistan and India due to widespread tabacco chewing. Familial clustering could be caused by familial chewing habits as well as genetic factors.

Non-Hodgkin's lymphomas are frequent in Pakistan for unknown reasons. Familial clustering would be caused by familial exposures to viral infections interacting with genetic immune dysfunctions.

Breast cancer forms 34 % of total cancers among females in Alexandria, Egypt, where 20 % of their parents are first degree cousins. A family history of breast cancer is the risk factor with the highest predictive value for breast cancer development world-wide. 5 to 10 % of all breast cancers are due to inheritance of highly penetrant

mutations in autosomal dominant susceptibility genes. Additional unknown genes are estimated to account for a similar or higher proportion of cases.

Ovarian cancer is the malignancy with the highest incidence of mutations in cancer susceptibility genes. 200 Pakistani women with ovarian cancer are studied for the presence of mutations by Dr. Imtiaz A. Malik, Karachi and Dr. Steven A. Narod in Toronto.

Gallbladder cancer is the major gastrointestinal neoplasm in Pakistan and other areas of Asia and Latin America and deserves an appropriate share of attention and resources.

A family history constitutes one of the most important risk factors for cancer. Therefore the patient workup in medical practice should include a carefully obtained family history. Persons at high cancer risk can be identified. Then they can be counseled and offered to participate in prevention and early detection programmes. The oncology nurse is part of the familial cancer clinic team. She collects, verifies and manages family information. She teaches, supports and accompanies the families.

Familial cancer counseling networks are developed in several countries. Dr. J. Utsunomiya in Tsuna is mutating the Japanese Polyposis Register System into a nation-wide network.

Cultural and social aspects of familial cancer differ widely between countries. Cancer and inherited diseases are feared in India and predictive screening may result in psychosocial problems for patients, families and doctors.

Cancer registries are a nucleus, sometimes the first, for new cancer control activities whereever they are established. Therefore UICC is giving increased importance to registry work.

Walter Weber, M.D.
March, 1999

UICC Familial Cancer and Prevention Project Meeting Woods Hole, USA, June 17-19,1999

Report

This meeting focussed on familial cancer clustering caused by interactions between infectious agents and genes.
One day was devoted to familial cervical cancer and half a day to familial gastric cancer (Add. 1). 17 Experts have participated (Add. 2).
M.M Burger has been a wonderful host (Addition 7). As a founding member of the UICC Familial Cancer and Prevention Project he pointed to the first Woods Hole Meeting in September 1992, where the UICC Family History Questionnaire has been presented for the first time by G.N. Stemmermann.

Familial Cervical Cancer

Human papillomavirus (HPV) infection is the cause of cervical carcinoma

There has been an general agreement on the most important fact that HPV infections are causally highly related with cervical carcinoma. H. zur Hausen pointed to the enormous heterogeneity of HPV viruses. The cellular reactions to viral infections are most important. Tumorvirusinfections interact with tobacco, sunlight, dietary mutagens, carcinogens, other infections and genetic factors. Epidermodysplasia verruciformis (226 400) and focal epithelial hyperplasia of the oral mucosa (136 400) are hereditary predispositions to papillomaviruses. HPV –DNA is integrated into cell-DNA and modifies it (e.g. interruption of intragenomic regulation). Persistent viral DNA can be reactivated by physical or chemical carcinogens etc. High risk HPV E6 and E7 genes are necessary for the maintenance of the malignant phenotype. High risk HPV (16,18) may act as solitary carcinogens. Links between MHC and cervical cancer remain controversial. Family studies should be done with two groups of women: those with cervical cancer and those with abundant cervical lesions. There is animal and human evidence for immune surveillance of papillomavirus infections. L1 and E7 are highly immunogenic. 6 vaccines are in development. Clinical trials have been started in 1997. In this year a first report from Taiwan showed that liver cancer occurrence can be reduced by Hepatitis B vaccination started in 1987. A global vaccination program with Hep. B+HPV vaccination would reduce cancer occurrence by 15 % in women and 10 % in men.

Cancer is not an infectious disease, but it may arise as a consequence of infection.

Primary Preventoin		Secondary Prevention		Therapy
Infection	---------->	CIN	---------->	Cancer
Age: 15		20		50

Cervical cancer control is possible now

According to Mark H. Schiffman cervical cancer is nearly understood. HPV16, 18, 31 + 45 cause ~ ¾ of cervical cancer. It occurs 50 times more frequently at the squamocolumnar junction than squamous cell carcinoma in vulva, vagina and penis. Bethesda Cytology Nomenclature: low grade squamous intraepithelial lesions (SIL) and high grade SIL. There are 3 stages of cervical carcinogenesis: 1. Women commonly get infected 2. Rarely HPV persists with progression to high grade lesions 3. Invasion. HPV id epidemic

Example: 2 Mio. ASCUS -------> 1 Mio LSIL -------> 300'000 HSIL -------> 15'000 CA
= infection = cancer precursor
Time is an intrinsic co-factor.

There are 3 major cohort studies: Portland Kaiser Permanente, Guanacaste Costa Rica and ASCUS – LSIL Triage Study
Costa Rica Cohort Study: registry data cannot be used, prospective, high grade lesions.

a) many high grade lesions and cancers can be found at a single screen (with well applied high-tech methods)
b) for HPV DNA testing a theshold of 1,0 pg/ml is about optimal
c) several interesting new screening combinations can be considered. Cervical cancer could be prevented now with money and high technology (just do it!) With one machine you can screen 2 Mio. women per year.

Risk factors

The search for important HPV cofactors for high grade SIL and cancer is likely to dominate future epidemiologic research on cervical cancer. HPV have a unique relation to p53 explained A. Storey. The two HPV oncoproteins E6 + E7 perturb cell cycle. Codon 72 polymorphisms are important in protein-protein interactions. E6 proteins are more variant at the amino acid level than E7 proteins. The theory is that cellular genes must be modified for HPV-linked carcinogenesis to occur.

J.J. Mulvihill concludes that exploratory studies for mechanisms should be done on population based samples. He presents his new book: Catalog of Human Cancer Genes, The Johns Hopkins University Press, 646 pages, 1999, ISBN 0-8018-4799-0

Cervical cancer is the most frequent cancer of women in Latin America

C. Santos, Peru: Half a million women get cervical cancer worldwide every year; 80 % occur in developing countries. 30 % of the affected women are in the reproductive phase. There are few population based cancer registries in Latin America. There are underdiagnosis, underregstration and wrong estimations of populations at risk. Lima: The Metropolitan Lima Cancer Registry counts 1100 cervical carcinomas per year (85 % invasive). Trujillo has a higher incidence rate. CIS peaks at 35 years. Smoking has little influence, but education. The prevalence of HPV is 20 % in CIS (HPV6 dominance) and 90 % in cervical carcinoma. In the same patient lymphnode metastases have the same HPV type as the primary cancer.
Lima collaborates with Yorktown university

M.Garces, Guatemala: The Guatemala Cancer League is building up a National Cancer Registry in Guatemala, where 50 % of the population has access to the health system. 50 % of the population are Mayan and 30 % Latinos. Life expectancy: 64 years in cities, 58 years in rural areas. Indios have lower frequencies of cervical cancers and high consanguinity.

S. Bejarano, Honduras: In San Pedro Sula (500'000 in habitants) a cervical cancer screening unit is existing since 30 years. Hospital bosed cancer registries are set up and expanding into their corresponding geographic areas.

Cervical cancer control is difficult

C. Santos: a cervical cancer control program failed in Peru because positive women were not treated. Screening should be associated to other programs (e.g. mother-child). Such a program has to be integrated into a local structure.

M. Garces: working in Central America is more difficult than in South America. Political support for health is minimal except in Costa Rica.

C. Sessa: a cervical cancer control program failed after a successful start in Nicaragua because of sudden with drawal of government support after a political change. Another program was successful: the La Mascota twinning programme for Childhood ALL (Masera G. et al. Lancet 1998; 352: 1923-1926). What is vital for such programs is a long-term commitment to a comprehensive strategy that incorporates supply of drugs, training and supervision of health professionals, and the care of the children and their parents.

UICC initiates a registry project

M. Almonte, Peru, presents the UICC Hospital-based Cancer Registry Pilot Project in Central America (Add. 3). Computers have been provided and a software has been developed.
Hospital registries are quite informative in small countries because travel distances are short.
Among future needs are: personnel recruitment, training in computer software, assistance for data collection and publication. UICC should implement a more epidemiological program in Central America.

First family history data in Latin America

A. Hildesheim: Costa Rica has a nationwide Cancer registry. In the Guanacaste Cohort Study a random sample of 11742 women have been included. A limited family history has been included asking for cancer of the reproductive organs in female first degree relatives. 2139 tests were abnormal. 6 % (120) of these women had a positive family history as defined above. 73 extended family history questionnaires were elicited. There is modest evidence for familial clustering of cancer of reproductive organs (Addition 4). Further family studies are needed. Other target populations could be:

1. Epidermodysplasia verruciformis. There is an ongoing study in France.
2. Young cases with limited latency since exposure to HPV. In the Guanacaste Cohort 10 out of 329 (3%) "normal onset" cases reported a history of maternal cervical cancer. 3 out of 43 (7%) "rapid onset" cases reported a history of maternal cervical cancer. Maybe the focus should be on young probands.
3. Women with high-grade squamous intraepithelial lesions (H. zur Hausen).

S. Bejarano has started to use the UICC Family History Questionnaire in Honduras. In the first 100 women interviewed she found a 8 % familial cervical cancer clustering.

Poject Proposal: Cancer in First Degree Relatives of Latin American Women with Cervical Carcinoma

W. Weber presents the protocol draft (Add. 5). There is general support for such a project. Guatemala (N.A. Garces) Honduras (S. Bejarano) and Peru (C. Santos) will participate. Each country will contribute cancer related family histories (first degree relatives) of 500 women with cervical cancer and 500 women without cervical cancer. The study will last 2 years and have a midterm evaluation. Dr. Chris de Wolf in Geneva will be the UICC representative because he is already collaborating with the national coordinators mentioned above in the hospital – based cancer registry pilot project in Central America. Dr. Davide Brunetti has agreed to take care of the statistics at the Trieste Cancer Registry with the support of Dr. L. Tomatis , former director of IARC in Lyon.
Study controls: M.A. Garces proposes to take them from the same neighbourhood where the patient lives. M. Schiffmann would also consider hospital controls (women in the next bed, in a general ward).
A. Hildesheim: taking controls from cervical cancer screening programs might introduce recall bias. Taking other cancer patients? A majority feels that this could also introduce recall bias. Other suggestions: spouse controls, affected pair analysis.
Questionnaire: a majority suggests to add 2 more questions: "total number of siblings and children?" (a control question) and "age at first intercourse?" (for finding rapid onset cases). A more extended questionnaire could comprise age at first marriage, number of sexual partners, date and cause of death, diagnosis verification, expansion of the predigree.

J.-M. Haefliger raised the points which have to be clear for the Swiss Cancer League: 1. Final questionnaire 2. Ethical approval 3. Budget 4. Participants. All four points have been evaluated, discussed and agreed upon. The Swiss Cancer League will be asked to make a major contribution. Collection of biological material: M. Schiffmann and A. Hildesheim make a strong plea for adding a collection of biological material, because this will be a unique study with a large sample of cases (n = 1500) and controls (n = 1500). Biological specimens could be blood or scrapings (cervical, vaginal, buccal). G.N. Stemmermann suggests to establish a central repository in Switzerland. Some kind of DNA specimens should be preserved like smears from cervix and vaginal wall. Serious consideration should be given to DNA collection because an opportunity would be lost. For data protection the samples would have to be anonymized.

Familial Gastric Cancer

G.N. Stemmermann gave a beautiful overview (Add. 6). Although most familial clusters of gastric cancer probably arise on the basis of shared kitchens and shared H. pylori infections, germline mutations account for a small proportion (1-2%) of these clusters. Polymorphisms may be working. If you change the two causes kitchen + H. pylori sporadic as well as familial gastric cancer will decrease.
75 % of the general population are infected by H. pylori and 5% of them get the tumor. There is an association with blood group A. Pepsinogen work should be extended.
M.A. Garces presented risk factors in Guatemala. A case – control study is addressing this question in collaboration with Costa Rica and Japan. The diffuse type histology is more frequent in women and in younger persons. The cancers are mostly distal; this is typical for poor countries. Poverty has more impact on intestinal than diffuse type histology (age at first pregnancy measures social class plus poverty). Fruits are protective. For genetics look at the diffuse type histology.
E. Payet presents data from the only cancer center in Peru with a 300 bed hospital built with cigarette tax. Stomach cancer is the most frequent cancer in males and the third most frequent cancer in females. 2990 cases came the Instituto Nacional de Enfermedades Neoplasicas in Lima from 1952 to 1996; half of them could be operated curatively. 2 pedigrees with 2 gastric cancers are presented. There were 250 cases of gastric lymphomas from 1952 to 1995.

P. Chappuis gives a comprehensive overview on familial gastric cancer syndromes (Add. 8). There is now clear for such syndromes. Characteristics are: diffuse type, early onset and strong family history. The biology is still poorly understood.

Conclusions of this Meeting

Family studies will be important for unraveling interactions between infections and genes in cervical and gastric cancer. A cervical cancer family history study will be started in Latin America in the year 2000 through UICC with the help of the Swiss Cancer League. The study will be added to the UICC hospital-based cancer registry pilot project in Central America and to ongoing cervical cancer preventive activities in Guatemala, Honduras and Peru. This first study will identify interesting families for future studies. If it has a successful start a gastric cancer family history study will follow.

Woods Hole/Bern

Walter Weber, M.D.

UICC Familial Cancer Project and International Oncology Conference

May 2 - 4, 2001, Beijing Hotel, Beijing, China

For the first time Familial Cancer has been the focus of a two-day national oncology conference in the capital of China. This première was possible thanks to the support of the Swiss Cancer League (SCL), the International Union against Cancer (UICC), the National Nature Science Foundation of China (NSFC), the Cancer Institute Chinese Academy of Medical Sciences (CICAMS), the China Cancer Research Foundation (CCRF) and the Society of Cancer Epidemiology Chinese Anti-Cancer Association.

China participates in the Human Genome Project and works on chromosome 3. Cancer is one of the main health problems in China (year 2000 without skin cancer) new cases: 1,15 mio. men and 0,75 mio. women; deaths: 0,87 mio. men and 0,49 mio. women). The leading cancer localisations in China are lung, liver, stomach, esophagus and colorectum in male and stomach, breast, lung, liver, esophagus, colorectum and cervix in female. Occasional familial clustering is observed in all of them.

Familial lung cancer is caused mainly by active and passive smoking. Several lines of evidence suggest that genes may also play a role and that individuals may differ in their susceptibility to the environmental insults. The best fitting model resulting from segregation analyses is a combination of cigarette smoking + random unmeasured factor + polygenetic factor + major gene.
In non-smoking women risk factors are exposure to fumes from cooking oil, passive smoking at workplace, lung cancer in the family and consumption of pickles.

Familial liver cancer is caused mainly by infections with hepatitis B and C viruses. These may interact with inherited susceptibility. Segregation analysis supports the existence of a recessive allele with population frequency 0,25 resulting in a lifetime risk of hepatocellular carcinoma of 0,84 for males and 0,46 for females.

Familial stomach cancer is caused mainly by diet and infection with Helicobacter pylori. Genetic predisposition is also important (see Caldas C. et al. J. Med. Genet. 1999; 36: 873-880). H.pylori seropositivity is associated with increased risks for gastric cancer in the Linxian Study (see Limburg P.J. et al. J. Natl. Cancer Inst. 2001; 93: 226-233).

Familial esophagus cancer is studied in Yangquan, Shanxi province. Mendelian autosomal recessive inheritance of a major gene that influences the susceptibility to esophageal cancer provides the best fit to the data (see Lee Carter C. et al. J. Natl. Cancer Inst. 1992; 84: 771-776). Exogenous risk factors are tobacco, alcohol and dietary components.

Tobacco smoking, unhealthy dietary habits, HBV and H.pylori infections are very prevalent among the general public in China. Measures targeted to reduce these risk factors and to enrich protective factors should be taken as the most crucial actions against cancer.

Familial cervix cancer is caused by human papillomaviruses (HPV) and possibly facilitated by familial disturbances of the immune system (Hemminki K. et. al.: Int. J. Cancer 82: 775-781, 1999). Family studies are initiated in Yangcheng Country, where cervical cancer rates are among the highest in the world.

Familial nasopharyngeal cancer NPC is studied in Southeastern China, where the disease is frequent. There is strong familial clustering. A genome - wide linkage analysis was conducted on 20 NPC families in Guangdong Province. There was linkage to a locus on chromosome 4. Epstein-Barr virus (EBV) is strongly associated with NPC and LMP-1 is the most important potential oncogenic EBV-encoded protein. EBV encoded RNA has also been found in T cell lymphomas in Beijing.

Many frequent malignancies in China are caused by **interactions between infections agents and host factors**. Cancer families are models of nature for risk factor studies with the methodology of genetic epidemiology and ecogenetics.

Taking the **family history** is a low technology method applicable all over the world to be used to identify persons at high cancer risk and to target appropriate preventive and therapeutic measures. It is known that relatives of cancer patients are susceptible to recommendations on prevention and early detection.

Ethics of cancer prevention has to take into account current debates in contemporary bioethics. A distinction is made between high-risk individual based interventions (e.g. screening in high-risk families) and population-based interventions (e.g. policies removing an environmental hazard). The Precautionary Principle has emerged in 1992 in the Rio Declaration. It states that 100% certainty should not be required prior to taking preventive action. It should be consistent with current theory and practice of evidence-based decision-making in epidemiology and preventive medicine.

Walter Weber

Further reading

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UICC 2003 International Conference Report

Family Cancer: Biology and Clinical Care

June 5-7, 2003. Oklahoma City, USA

written by

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UICC 2003 International Conference Report
Family Cancer: Biology and Clinical Care
June 5-7, 2003. Oklahoma City, USA

The **objective** was to present and discuss latest research findings on familial cancer.
The 120 **participants** encompassed laboratory researchers, clinicians and counselors.
The **conference** was composed by a fruitful mixture of update and controversial plenum presentations, interdisciplinary panels, working group sessions, poster sessions and exhibits. Lessons and insights were drawn form ongoing work with families.
Included in the **social program** were a gala with an authentic Native American Tribal Dance, a reception at the National Cowboy and Western Heritage Museum and a dinner reception in a private home with the Board of Children's Medical Research Institute of the University of Oklahoma Health Sciences Center.

Oligogenic Disorders

Neurofibromatoses

A. Sørensen gave an overview. Only 30% of the mutations can be detected in NF1. Plexiform neurofibromas may become malignant, but not dermal neurofibromas. Animal models show that NF1 mutations are not sufficient for NF1-syndrome. Family studies remain important for defining the syndromes and for phenotype-genotype correlations.

Cowden Syndrome

C. Eng reminded that affected persons look like everybody else. They have breast cancer and epithelial thyroid cancer. In 80% mutations are found in PTEN. There is a cluster in exon 5.
PTEN mutations are also found in BRRS (60%), Proteus syndrome (20%), Proteus like syndrome = "Elephant Man Disease" (50%).
Preventive measures: genetic counseling and testing; annual physical exam + mammography + sonography of the thyroid.

Fanconi's anemia (FA)

FA is the most frequent and most thoroughly studied of the rare inherited bone marrow failure syndromes (IBMFS). In 1927 G. Fanconi reported three brothers with a progressive lethal anemia and brown pigmentation of the skin.

So far 10 FANC genes are known. The most frequent is FANC G – a huge gene ("the geneticist's nightmare"). All IBMFS leukemias are myeloid. There is a 50-fold increased cancer risk. The primary risks are: 53% aplastic anemia. 10% AML and 30% solid tumors (oropharynx, esophagus, vulva, anus, cervix, brain etc). They occur at early age.

Gorlin Syndrome

R. Gorlin reviews the syndrome named after him. It is also known as the Nevoid Basal Cell Carcinoma Syndrome (NBCCS). Mechanisms of carcinogenesis and teratogenesis can be studied. Radiotherapy can induce basal cell carcinomas and meningiomas. Hit one is inherited (1:60'000). Gene carriers are born with multiple minor malfomations. R. Gorlin and C. Eng are looking for Maffucci syndromes.

Li- Fraumeni Syndrome (LFS)

LFS comprises more cancer sites than originally reported (e.g. tumors of chorionic plexus; animals get oligodendrogliomas). p53 was discovered in 1979. D. Malkin oversees 185 families with germline p53 mutations. Percentage of p53 mutations:

LFS 75-100%, LFS–L 10-15%, sporadic ADCC 50-80% (Brazil: Arg 337 His mutation), RMS 10-15%, OS 5-10%, second neoplasms 5-15%, early onset breast cancer 1%. Maybe p53 is BRCA3. p53 is inactivated in LFS. SV40 T-Antigen inactivates p53. D. Malkin and F. Li did the first presymptomatic testing in children.

Surveillance is done with clinical examination, laboratory and imaging.

Site Specific Familial Cancers

Familial Colorectal Cancer

Colorectal Cancer (Crc) has increased in Japan. The risk is reduced by vegetables/ fruits, NSAIDs, Calcium, hormones (exogenous and endogenous) and physical activity.

J. Potter discussed the influence of polymorphisms on crc risk . NAT and heterocyclic amines probably play no role. They are associated with smoking. Of interest are microsomal epoxide hydrolase (EPHX), reduced folate carrier polymorphisms and thymidilate synthase. The activation of aspirin may be important. There probably are polymorphisms who matter in adenomatous and hyperplastic polyps . There is a growing suspicion that hyperplastic polyps of the serrated type are precursors of cancer. Environmental factors cause somatic gene changes and epigenetic changes.

FAP: H.T. Lynch, Omaha, gave an overview. The first recorded patient dates back to 1721.

HNPCC (Lynch Syndrome)

HNPCC dates back to A. Warthin. H. T. Lynch pointed to the preventive and therapeutic potential of prophylactic colectomy and prophylactic hysterosalpingo-oophorectomy. Despite worse prognostic factors, HNPCC has a better prognosis than sporadic colorectal cancer. But carcinogenesis is accelerated (2-3 years from adenoma to carcinoma) . Therefore colonoscopy should be done every year. "Get the families together and inform them. They all appreciate it". In HNPCC there is a strong infiltration by lymphocytes.

A. de la Chapelle reported on his large scale screening study in Ohio supported by NCI (D. Seminara). In analogy to the Finnish data 900 mutation positive persons can be expected to be identified in Ohio every year (how are they going to be managed?). The calculations work: HNPCC is found like in Finland. 50% are missense mutations, making an interpretation most difficult. Sometimes the protein is lost (→ immunehistochemistry). Many problems can be resolved by allele separation. The compliance is 70%. Mutation analysis in the stools will probably come. The phenomenon is real. A problem is: most of the DNA stems from normal cells; only little is from tumor cells. The term "HNPCC" concentrates too much on the colon. "Lynch syndrome" would be more adequate. Lung and prostate cancer are not part of it. MSI determination is easy with fluorescence sequencer. It is still not known if you have more mutations in the Vogelgram genes. Genes encoding important micro-

satellites may explain the multiple organ involvement. 85% of crc have chromosomal instability; 15% are MSI + (1/3 Lynch syndromes, 2/3 gene silencing). Colonoscopy screening works: in Finland 133 mutation carriers were screened every 3 years: 8 crc and no deaths. 119 were not screened: 19 crc and 9 deaths (observation period of 15 years; see Järvinnen et al. 1995 + 2000).

It is desirable to identify carriership of MMR. Passive approach: genetic evaluation of cancer patients and families displaying risk features. Active approach: population screening.

There is MSI in nearly 100% of Lynch syndromes. If positive: look for germline mutations. This was done in Finland: n= 1044 → 129 MSI+ = 12% → 28 mutations=2,7% (underestimate). There were founder mutations in MSI+ but not in MSI-. Calculations for Ohio: 5600 new crc per year → 750 MSI+ → 150 mut+ → 150 Lynch syndromes → 1500 at risk → 750 mut+ → 150 + 750 = 900 mut+ in Ohio every year.

H. Hampel discussed counseling issues in HNPCC : 1.Variants of unknown significance. 2. Different interpretations of mutations. 3. Noncompliance. 4. Insurance issues. 5. Phenotypic overlap. 6. Mirosatellite stable cases. 50% of mutations are missense mutations. There is the need for a group to take care of them (ev. NCI sponsored).

Familial Gastric Cancer

There is a role for prophylactic gastrectomy. G.N. Stemmerman points to the fact that most family clusters arise from shared household exposures to known risk factors such as H.pylori, smoking, high salt and nitrate intake, low intake of fresh fruits and vegetables. The Napoleon family is typical: subsequent generations had no gastric cancers any more and the localisation of the cancers were typical for sporadic cases. Several genetic polymorphisms have been identified that enhance, or reduce, the level of risk generated by the different environmental hazards. Stomach cancer families share more polymorphisms than non-cancer families. In hereditary stomach cancer due to germline E-cadherin mutations there is a role for prophylactic gastrectomy.

Familial Pancreas Cancer

The National Pancreatic Cancer Registry has been started by J.J. Mulvihill in 1988. 106 families have been enrolled so far. C.E. Aston presents the inclusion criteria:
1) at least two first-degree relatives with adenocarcinoma of the exocrine pancreas or 2) two affected second-degree relatives connected by a relative with any type of cancer.

Further organisations: The National Familial Pancreas Tumor Registry (1 cancer, 1000 families). Pancreas Cancer Family Registry (H.T. Lynch). EUROPAC. Seven new registries have been started (Toronto, Madrid, Indiana etc.). Action Network : www.pancan.org. The best model fits a dominant mode of inheritance. Pancreas cancer is also part of other familial cancer syndromes like HNPCC, FAP, FBC, FAMMM, MEN1, VHL, Li Fraumeni Syndrome etc.

The University of Oklahoma Health Sciences Center starts an anthropological study, where the investigators will live with cancer patients. Potential opportunities are: Identification of a major gene à la breast cancer, of gene-environmental interactions and of risk people for screening.

Familial Breast Cancer (FBC)

FBC dates back to Broca. It is often associated with other primaries. The Madrid conference was somewhat disappointing. No promising linkage has been found after BRCA1 and 2. Low penetrance genes will have to be searched in ethnic groups. Collaboration with partners in other countries and better links with the developing world are needed. J. Balmana reports on 245 breast / ovarian cancer families, where 19 BRCA1 and 19 BRCA2 mutations have been identified. The recurrent BRCA2 mutation 9254 del ATCAT is found in Catalunya. The R71G BRCA1 mutation is a deleterious Spanish founder mutation in Galicia. According to C. Corvello there is a very low BRCA detection rate in Brazil. O. Olopade reminds us that we still need to collect families (e.g. ASCO). There are the same mutation rates in breast-ovary families in Africans, Caucasian and Ashkenasy Jews. Testing should be offered to everybody. Awareness is needed of early onset cases, no. of breast cancers in the family, association of breast and ovarian cancer.

BRCA – associate tumors require loss of both alleles plus additional genetic events.

S. Neuhausen is asking now: is there another high penetrance gene or are there all low penetrance genes? There is the CHEK 2 1100delC mutation in 5,1%of non BRCA breast cancer families leading to a 2-fold increase of breast cancer in women. One should still try to identify a high penetrance gene by a genome wide search. BRCA1 was found because of the breast-ovarian association and BRCA2 because of male breast cancer.

Further avenues: stratification by phenotype, population-based and family- based (spouse as co), gene-gene interactions, pathways, incorporation of other risk factors into models for analysis.

InterGenetics Inc. in Oklahoma City (www.intergenetic.com) is building a polygenic risk evaluation test for breast cancer derived of a large population based series, collected in Oklahoma City and Kansas City. Information on genetic analyses is combined with personal history measures. Common alleles of SNPs are examined with individual low penetrance for risk.

Familial Melanoma

H. Lynch reports that pancreatic cancer is now appearing in the melanoma families (FAMMM-Pancreatic Cancer Syndrome, see Lynch et. al. Cancer 2002; 94: 84 – 96). Mutations in CDKN2A (p16) are identified. One patient had 15 malignant melanomas. There is also a hereditary variant of intraocular melanoma.

Familial Prostate Cancer

J. Trent (Translational Genomic Research in Phoenix, AZ) reports on the search of prostate cancer genes within ICPCG. The HPC Family Database has been started in 1992 together with Johns Hopkins. 8 + loci are implicated. HPC 1 on 1q24 has been cloned and confirmed in 2002. MSR1 is expressed in macrophages indicating that infection has an important role. The X chromosome locus (Xq28) is frequent in Finnland.

Family history is still the most important risk factor. One has to look at thousands of families. Consortia are needed. This is a duty for NCI.

Prostate cancer and breast cancer are frequent in Barbados (250'000 inhabitants, 98% African). Gene expression and DNA sequence variations have to be integrated. An Applied Nano Bioscience Center is needed.

Familial Testicular Cancer

E. Rapley reports on behalf of the International Testicular Cancer Linkage Consortium (ITCLC) established in 1994. There are ethnic differences in incidence and lack of its change with migration. Highest incidence in Swiss and Maoris. Risk factors: Family history, previous TC, undescended testis, infertility and testicular dysgenesis. 326 pedigrees have been identified. 220 are fully collected and genotyped. 180 are analyzed. TC is transmitted through women in 99 families. There is linkage of TGCT1 to a region on Xq27, which has been sequenced and annotated at Sanger Center. TC risk is lower to sons than to brothers. Further candidate regions: 18q22-qter (recessive model), 3q27 (recessive model), 16p13 (dominant model), 12q12-q13 (recessive model, one big family).

Ecogenetics

The term "ecogenetics" has been introduced into the cancer arena by J.J. Mulvihill (in: Familial Cancer, Karger Basel, pp 13-16, 1985). It refers to heritable variations in response to environmental exposures. Determinants of pancreatic cancer are studied through an interdisciplinary approach in families of the National Pancreatic Cancer Registry at NCI. There is a possible excess of breast and stomach cancers but not lung or colorectal in pancreatic cancer families.

N. Shimke points to the fact that tumor types change in the families of different countries and over time. In Turkey families homozygote for mLH1 have lymphomas and leukemias.

Endocrine Neoplasia Genetics

MEN 2 (RET mutations). According to L. Mulligan mutations show tissue specific penetrance. Genotype determines the aggressiveness of disease and age at which MTC is identified.

Prophylactic thyroidectomy is recommended at age 6. H.T. Lynch proposes testing at birth (cord blood) and prophylactic thyroidectomy at age 3 in MEN 2B and at age 5 in MEN 2A by a highly experienced surgeon.

MEN1

S. Marx points to the fact that still little can be done in prevention and therapy.

MEN	1	2
High cancer mortality	YES	YES
Test gives good information	YES	YES
Test blocks cancer	NO	YES

MEN 1 +/- mouse has no gastrinoma, frequent pheochromocytoma and giant hyperplastic islets. Possible mechanism: menin inhibits transcription activated by JunD.

NCI lab finds mutations in 90%. There are families who have linkage but no mutation. Reasons could be deletion, intron or promoter mutation.

Carney Syndrome

B. Stratakis distinguishes between Carney Complex (CNC) and Carney Triad. CNC is a MEN. 2/3 have thyroid pathology (10% carcinomas). 10% have pituitary hyperplasia and acromegaly.

Two genetic loci are involved (on 2p and 17q). CNC is the first human disease found to be caused by mutations of one of the subunits of the PKA holoenzyme, a critical component of numerous cellular signaling systems.

The highest risk are cardiac myxomas. Yearly echography should be started in the first year of life. Myxomas outside of the heart (skin, breast) and sertoli /Leydig cell testicular tumors should not be operated.

Hereditary Paraganglioma

Hereditary paragangliomas (MIM 168'000) are usually benign slow growing tumors of the parasympathetic nervous system. AD inheritance with reduced penetrance. 10-40% have a familial background. 10% are malignant. Germ line mutations in SDHB, SDHC and SDHD encode subunits of the mitochondrial complex II. There is maternal imprinting. P. Devilee reported on a Dutch founder effect at SDHD. If the tumors are at the base of the skull, the symptoms are: pulsatile tinnitus + hearing loss + facial

nerve paralysis. Diagnosis: MRI. Tumor doubling time: 10 years. The tumors are highly vascularized. Surgery is therefore very delicate. Radiotherapy is only palliative.

Clinical Assessment, Counseling and Testing

Family recruiters are needed. This new profession consists of a professional between nurse and a genetic counselor. A 2-year education is required. Infrastructures to collect families have to be built. Getting the samples is difficult.

The Cancer Risk Evaluation Program (CREP) of the University of Pennsylvania is presented by J. Stopfer. The first appointment is given after the completed questionnaire has been returned. The Progeny computer program is used for conspicuous families. Oncologists prepare most of the information. The principal of non–directive counseling is currently being challenged, because it is not appropriate in many situations in cancer genetics clinics. People often want an opinion for informed decision making. Global distress or anxiety is not increased in BRCA1/2 mutation carriers compared to other people at high cancer risk. Once a mutation has been found, those declining testing are more likely to be distressed.

S. Kieffer reports that services are centralized and publicly financed in Canada. The budget is the limiting factor. There may be long waiting lists.

In Brazil the test result belongs to the patient and cannot be given to a physician without his consent.

Kelly Metcalfe, a nurse-counselor with an amazing publication list, reports that genetic testing does not increase the level of distress and that there is a higher post test level of intrusive thoughts. 22% to 50% over-estimate their risk after counseling. Over time this percentage goes up. 84% of persons to whom genetic testing is recommended want to do so. 60% of BRCA1 family members requested results after the baseline interview. 28% felt they had not received enough information about prophylactic surgery. Over half of the men with a known BRCA1/2 mutation want gene testing because of their daughters. 15% of mutation carrier never heard of tamoxifen. 72% wanted to learn more about tamoxifen. 58% physicians have not provided enough information. More carriers elect prophylactic surgery than taking drugs. Prophylactic mastectomy: USA 35%, Australia 8%, and Canada 65% consider it; USA 0-3%, Canada 15%, and the Netherlands 54% have it.

A working group identified the following **problems and needs:** 1. mutations of unknown significance. 2. repositories 3. more cancer genetic specialists 4. education of doctors 5. expand service to follow-up 6. reimbursement 7. referral guidelines, public outcome data 8. support public health efforts to incorporate family history to become standard of patient care 9. increase marketing of cancer genetic services.

Research Infrastructure and International Collaboration

Apart of clinical based studies, the analysis of cancer risks for relatives of index cases in analytic–epidemiologic studies and apart of twin studies there are population based studies like in Iceland (0,2 mio. inhabitants), Utah (1 mio. inh.) and Sweden (20 mio. inh.).

Statistics: Sweden has linked a Multigeneration Register covering 5 generations (started 1955) to the Swedish Cancer Registry (started 1958). This Family–Cancer Database has been used in 140 studies so far. K. Hemminki reported that recessive effects probably play a role in kidney and testicular cancer. Increase in familial risk depends on histology . The strongest familial association is found between breast cancer and oligodendroglioma.

The consortium approach was presented by D. Seminara : Collaboration of clinical and laboratory researchers within consortia are useful for the identification of new cancer susceptibility genes, the ascertainment of causes and new therapies. Collaboration is facilitated; subset analyses and data sharing is made possible. D. Seminara informed on The Family History Public Health Initiative (FHx-PHI) of the CDC in Atlanta (http://www.cdc.gov/genomics/info/conference/famhist.htm). Family medical history represents a "genomic tool" that can capture the interactions of genetic susceptibility, shared environment, and common behaviors in relation to disease risk. This new initiative will evaluate the effectiveness of family history for assessing risk of common diseases and influencing early detection and prevention strategies. D. Seminara also presented Cancer Family Registries available to investigators to conduct population and clinic-based interdisciplinary research, with a main focus on the genetic and molecular epidemiology of these cancers. (www.cfr.epi.uci.edu).

M. Foster, an anthropologist, presented the International Hap Map Project. Haplotype blocks are conserved in populations. DNA samples from named populations in US, Nigeria, Japan, China and Europe are collected for genotyping (Haplotype – Tag SNP's). They are public resources for everybody incl. private industry. Ethical challenges are: differing standards, ev. future risks of cell lines, risks to individuals. Social identifiers matter. Danger: genetic essentialism. Starting with social identification may end in biological dogmata. Close collaboration with local politicians, social groups etc. Everything goes on the net immediately.

R. Sijmons presented the Familial Cancer Database (www.facd.info). The new version 2.0 will be released to the public in autumn 2003. Facd is for downloading into your personal computer.

C. Stratakis recommended to redirect to rare diseases such as endocrine tumor syndromes where still a lot can be learned.

100 mio. dollars have been spent for familial cancer research over the past 10 years. Thousands of families are in data bases. They are gold mines for future use, but they will have to be managed. A newer national standard of coding is needed. Treatment related genetic research is done by the pharmaceutical industry. Proteomics will use samples for identifying high risk groups. Big groups should collect family histories as part of the data. A priority is defined: database + adequately trained people + whatever that means + mechanisms of ethics. Combining recruitment in the developing word with information orientation might be an attractive project for the Bill Gates Foundation. In all Nordic countries Guthrie spots are stored indefinitely. Blood spots last for "ever".

A working group identified the following **problems and needs**: 1. Mechanisms to achieve the goals: registry/directory of studies, directory of investigators, enhance the gene test database, co – morbidity registries (eg HTLV-1, HBV etc.) that relate to carcinogenesis, interesting families registry à la R. Gorlin. 2. Minimal Data Set Information. 3. International Family Cancer Database (proposed to NHGR I – ELSI) 4. Partners: Nat. Library of Medicine, Consortia, NGO, NIH Programs. 5. Platforms for Communication : a) Letter of the Editor as part of meeting proceedings in e.g. AJHG, Ca Res and JCO. b) Platform of oncology + genetics + infectious diseases. c) Consider a second meeting, e.g. in Toronto with joint sponsoring (NIH Conference Grant Funding + others).

Conclusion

The participants agreed that a family medical history should be elicited in every person worldwide and be used for downstaging diseases. Within the next 10 years infrastructures should be built to collect families. Data base management has to be developed. Collaboration with consortia and partners in other countries are needed. Better links to the developing world have to be established. Samples of biological material have to be collected and administered. We should look at low penetrance genes, ethic groups, high risk groups, rare diseases and tumors due to infections. Adequately trained people are needed to recruit families. Ethical, legal and psychosocial aspects have to be studied. Familial cancer specialists, geneticists, oncologists and infectious disease people should collaborate as equal partners. Their societies should sponsor future meetings.