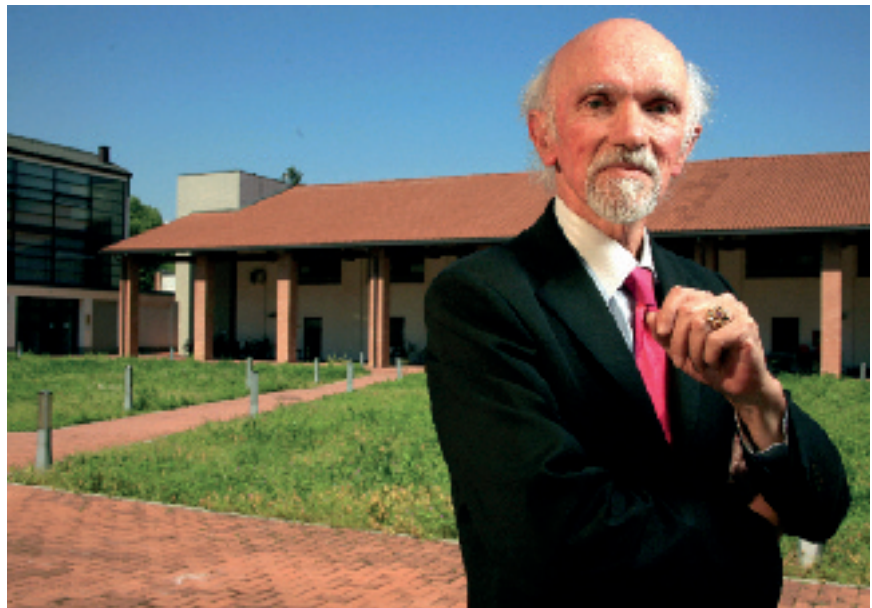


PREVENTIVE AND PREDICTIVE MEDICINE DEPARTMENT



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UNITS

EPIDEMIOLOGY AND PREVENTION

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Vittorio Krogh

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Gemma Gatta

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Paolo Radice

MOLECULAR BASIS OF GENETIC RISK, POLYGENIC MODELS

Tommaso Dragani

This Department focuses primarily on epidemiological and translational research. This comprises knowledge of lifestyle and genetic risk factors in order to take preventive action (i.e. from prediction to prevention), and knowledge of inequalities in cancer treatment for carrying out corrective actions. This research relies on extensive interaction between researchers in the fields of basic experimental science, epidemiology, genetics, and clinical medicine.

The priorities of the Department are:

- promotion of healthy diet and lifestyle: to proceed from large cohort studies in which the INT has been actively involved for more than 20 years, to dietary intervention studies targeting the general population, high-risk subgroups and cancer patients to minimize the risk of recurrence
- environmental and occupational risk factors: this research is moving from standard epidemiological designs to the systematic monitoring of occupational risk through the linkage of cancer registry data and occupational history files, in addition to forming stronger collaborations with the public agencies that are responsible for occupational and environmental surveillance in order to establish specific preventive actions
- hereditary cancer prevention in high-risk families: to go beyond clinical surveillance and prophylactic surgery, and promote research on environmental and lifestyle factors as well as genetic characteristics that may affect the penetrance of hereditary cancer genes
- in the field of low penetrance cancer genes and polygenic inheritance: to classify the complex genetics of risk and prognosis of lung and breast cancer
- inequalities in survival and cure rates of cancer patients: from the systematic description of cancer incidence, prevalence and survival, to research on the interpretation of survival differences between and within countries, and advance actions to minimize such inequalities.

EPIDEMIOLOGY AND PREVENTION

HEAD

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TECHNICIANS

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Daniela Del Sette Cerulli

ADMINISTRATIVES

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Grazia Guerrini, Maria Larossa

The Unit has two main research activities: 1) dietary and life-style intervention trials aimed at the prevention of breast cancer (BC) and of BC recurrences, and 2) observational studies on the relationship between metabolic and endocrine parameters and the incidence of BC and BC recurrences. The main ongoing study is the DIANA (DIet and ANdrogens)-5 project: randomized controlled trial to test the efficacy of dietary change and physical activity to prevent or delay the development of recurrences in BC patients estimated to be at high risk based on their hormonal or metabolic milieu. Study design: a) recruitment 2000 patients aged 35-70, operated for BC in the last 5 years, without recurrences, but with high serum levels of testosterone or insulin, in 8 collaborative centres in different Italian regions (Lombardy, Piedmont, Emilia, Abruzzo, Campania, Basilicata, and Sicily); b) randomisation in a control group that receives only general lifestyle recommendations for cancer prevention and in an intervention group that is helped to change through periodic meeting, kitchen and fitness courses, common meals, with decreasing intensity schedules over 5 years; c) follow-up the cohort for 5 years; analysis by intention to treat and by compliance score. By December 2010 1,200 patients were randomised.

Further studies include:

- A prospective study on several thousand BC patients admitted to INT for primary surgical treatment to test the prognostic role of androgens in BC progression. A biological bank of fasting blood samples collected at the time of diagnosis is available for BC researches.
- A pilot trial of metformin and diet for the prevention of breast cancer in 400 peri- or post-menopausal women with anthropometric or metabolic traits of metabolic syndrome. Factorial design: metformin versus placebo (double blind) and dietary intervention with kitchen courses and common meals versus dietary recommendations only.

Keywords: diet, breast cancer, metformin, intervention trial

2010 RELEVANT NOTES

Publications

Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. *Lancet Oncol.* 2010; 11: 530-542.

Urinary 6-Sulphatoxymelatonin levels and risk of breast cancer in premenopausal women: the ORDET cohort. *Cancer Epidemiol Biomarkers Prev.* 2010; 19: 729-737.

Contributions

Pasanisi Patrizia, Master in Nutrition, Università Politecnica delle Marche

Eleonora Bruno, Master in Epidemiology, University of Turin



NUTRITIONAL EPIDEMIOLOGY

HEAD

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Sara Grioni, Nutrition Tech, BSc

Maria Valeria Pala, Agronomy D, PhD

Sabina Sieri, Biol Sci D, PhD

ADMINISTRATIVE

Gloria Bosco

The Nutritional Epidemiology Unit is involved in large prospective studies on the association between diet, hormones, nutrition, lifestyle, genetic factors and cancer risk.

1. The EPIC study (<http://epic.iarc.fr>) was designed to investigate the relationships between diet, nutritional status, lifestyle and environmental factors and the incidence of cancer and chronic diseases. EPIC has recruited over 500,000 individuals in 10 European countries. The major published results during 2010 include: i) higher plasma levels of vitamins B2 and B6 are associated with a lower risk of colorectal cancer; ii) an increased risk of endometrial cancer with estrogen-only hormone therapy (HT) and a weaker association with combined HT; iii) obesity is an important modifiable risk factor for epithelial ovarian cancer; iv) serum levels of vitamin B6 and methionine are inversely associated with an increased risk of lung cancer; v) a genome-wide association study in pancreatic cancer identified loci associated with increased susceptibility on chromosomes 13q22.1, 1q32.1, and 5p15.33; vi) tobacco smoke (both active and passive) is associated with an increased risk of pancreatic cancer.
2. The ORDET study, one of the first prospective European studies on the role of hormones and DiET in the aetiology of cancer, was organized within the Epidemiology Units of the INT. During 2010, the main results from ORDET were: i) metabolic syndrome is an important risk factor for breast cancer in postmenopausal women; ii) there is a positive association between aMT6s and the risk of breast cancer in premenopausal women.
3. The ORDET study is participating in the "Pooling Project of Prospective Studies of Diet and Cancer" (<http://www.hsph.harvard.edu/poolingproject/about.html>). This collaborative project involves major European and North American cohort studies (at present 28). The main results in 2010 were: i) a modest inverse association between folate, vitamin C and E intake and colon cancer; ii) drinking coffee or sugar-sweetened carbonated soft drinks was not associated with an increased risk of colon cancer.

Keywords: prospective study, diet, hormones

2010 RELEVANT NOTES

Collaborations

Epidemiology of endometrial cancer consortium (E2C2)

The Pooling Project of Prospective Studies of Diet and Cancer

Endogenous Hormones and Breast Cancer Collaborative Group

International Lung Cancer Consortium

IDEFICS Consortium

IMMIDIET Consortium

Publications

A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet.* 2010;42:224-8.

Serum B vitamin levels and risk of lung cancer. *JAMA.* 2010;303:2377-85.



EVALUATIVE EPIDEMIOLOGY

HEAD

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Giulia Zigon, Statistician

TECHNICIANS

Rossana Berruti

Samba Sowe

The Unit is currently estimating the incidence, mortality and prevalence for several common tumors. In Italy, the burden of cancer is known only in areas covered by cancer registries. However, with the application of appropriate statistical models the basic indicators at the national and regional level can be estimated.

The Unit also has a principal role in assessing the burden of cancer in populations, focusing on rare tumors. Along these lines, the project "Surveillance of rare cancers in Europe" (RARECARE) will estimate the burden of rare cancers for which no estimates were previously available. The project takes advantage of a large database of cancer cases collected from population-based cancer registries in 21 countries. Based on the RARECARE definition (incidence <6/100,000/year), the annual incidence of all rare cancers in Europe was about 97 per 100,000, corresponding to 488,000 new diagnoses annually or 19% of all cancer diagnoses (www.rarecare.eu).

The study of cancer survival among children, adolescents and young adults (AYA) can determine whether differences found in EURO CARE for adults were also present in AYA. Despite the higher cancer incidence in the 15-30 age group compared to children, with only modest survival improvement, no specific consideration is given to the treatment of AYA patients with respect to their elderly counterparts.

The unit collaborates with the CONCORD (World Comparison of Cancer Patient Survival) study, which investigates differences in Europe, North America, Australia and Japan. The major objective of 2010 was to interpret variations between Europe and the US for colorectal, prostate, and breast cancers.

The AIRC funded project "Prostate cancer survival patients in Italy" will study variabilities in Italy by applying cure survival models that will separately estimate the proportion of cured patients and the life expectancy of cases who die of disease.

Keywords: rare cancers, cancer in adolescents and young adults, burden of cancer



2010 RELEVANT NOTES

Collaborations

Tropical Medicine, LSHTM, London, UK

Center for Disease Control and Prevention, CDC, Atlanta, USA

Fundacao Oswaldo Cruz, Rio de Janeiro, Brazil

Publications

Patterns of care for European colorectal cancer patients diagnosed 1996-1998: a EURO CARE high resolution study. *Acta Oncol.* 2010; 49:776-83.

The burden of rare cancers in Europe. *Adv Exp Med Biol.* 2010; 686:285-303. Review

Contributions

Referee for several journals (G. Gatta) during 2010 for papers submitted to *CMAJ*, *Ann Oncol*, *Eur J Cancer*, *Int J Cancer*, *Br J Cancer*, *Orphanet Journal*
G. Gatta, Member of the EUCERD (European Commission of Experts on Rare Diseases)

ANALYTICAL EPIDEMIOLOGY

HEAD

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Pamela Minicozzi, Mathematics D, MSc
Carmen Tereanu, MD, MSc

ADMINISTRATIVE

Chiara Margutti

The main activity of the unit consists in the analysis of cancer survival data and in the interpretation of differences across countries over time, within the framework of EUROCCARE (European CAncer REgistry based project on survival and care of cancer patients). EUROCCARE started in the 1990s and has produced 4 monographs (cases diagnosed in 1978-84, 1985-89, 1990-94, 1995-99) and numerous scientific publications. EUROCCARE-5, relative to patients diagnosed after 2002, is in progress.

The unit is responsible for the EUROCCARE scientific secretary and, in collaboration with the Istituto Superiore di Sanità, Rome, contributes to data management and statistical analyses. The unit is responsible for data collection and analyses of the EUROCCARE high resolution (HR) studies, designed to understand survival differences across regions and over time. The cancer registries participating in EUROCCARE HR collect detailed clinical information on tumor stage, diagnostic exams, tumor gene expression, treatment, follow-up, and comorbidities that influence survival. The HR studies describe, compare and monitor patterns of cancer care across European countries/regions, developing indicators of best practice and analyzing the effect of innovative diagnostic procedures and treatment in current clinical practice. Presently, studies are in course on breast, colorectal and lung cancer, as well as lymphoma and melanoma.

The Unit is responsible for HAEMACARE, a project aimed to investigate epidemiological and clinical indicators for hematological neoplasms in Europe.

The unit also collaborates with the CONCORD project (a worldwide study on cancer survival) that is led by Prof. MP Coleman, LSHTM, London (UK). Dr. Milena Sant is project leader of the Work Package 4 (Health information) of the European Partnership Against Cancer. In addition to population-based analyses, the unit carries out studies on clinical cohorts of patients to investigate the prognostic role of tumor characteristics and metabolic factors.

Keywords: survival, prognosis, population cancer registries, patterns of care, public health

2010 RELEVANT NOTES

Collaborations

Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Rome

IARC, International Agency for Research on Cancer

LSHTM, London School of Hygiene and Tropical Medicine

AIRTUM, Italian Association of TUMor Registries

FRANCIM, FRANce Cancer Incidence et Mortalité

ENCR, European Network of Cancer Registries

ICBP, International Cancer Benchmark Project, UK

EUROCCOURSE, EUROpe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research

EUROCHIP, EUROpean Cancer Health Indicator Project

Publications

Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010; 116:3724-34.

Variation in 'standard care' for breast cancer across Europe: a EUROCCARE-3 high resolution study. *Eur J Cancer*. 2010; 46:1528-36.

Contributions

Manual for coding and reporting haematological malignancies.

Tumori 96: i-A32. (M. Sant, co-editor)

MEDICAL GENETICS

HEAD

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RESIDENT

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ADMINISTRATIVE

Caterina Spina

The consolidated activity of the Medical Genetics Unit offers genetic counselling for several hereditary predispositions to cancer syndromes. The main focus of the Unit is the study of hereditary breast and ovarian cancer syndrome (HBOC), in addition to other inherited predispositions to cancer such as Li-Fraumeni syndrome and familial melanoma.

The principal goal of the Unit is to identify individuals at genetically increased risk of cancer in order to offer targeted clinical management by providing an integrated and multidisciplinary healthcare service. More than 6,550 individuals belonging to about 3,150 different HBOC families have been identified and characterized. When available, all relevant data has been collected in the Medical Genetics HBOC database (including more than 870 BRCA1 and BRCA2 gene carriers from over 470 families). Moreover, about 550 healthy and 450 affected women are regularly followed in collaboration with other INT Units.

All clinical, genetic, and molecular data of individuals belonging to HBOC families is constantly updated. For all patients treated at INT and followed by the Medical Genetics Unit, tumor specimens and blood samples are routinely collected.

The availability of familial, molecular, clinical and pathological data, as well as biological specimens, is essential for the following studies:

- genetic characterization of HBOC: gene penetrance, survival, disease features, as well as environmental risk factor modifiers and tumor characteristics
- long-term efficacy, health and psychological impact of clinical and instrumental surveillance, risk-reducing options and treatment in HBOC individuals
- biological and clinical significance of BRCA gene mutations of unknown risk
- genomic and transcriptomic analyses for the identification of modifiable risk factors and new genes involved in genetic predisposition to HBOC

Keywords: hereditary breast and ovarian cancer, cancer predisposition syndrome, familial and hereditary cancer

2010 RELEVANT NOTES

Collaborations

Breast Cancer Consortium (BCAC)

Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

Medical Genetics, Department of Medicine, Surgery and Dentistry, University of Milan

Hereditary Breast Cancer Clinical Study Group

Department of Oncology, Sacco Hospital and Fatebenefratelli Hospital (Project: Development of a model for the identification and management of women at high genetic risk for breast cancer, PI: S. Manoukian)

Publications

Four new cases of double heterozygosity for BRCA1 and BRCA2 gene mutations: clinical, pathological, and family characteristics. *Breast Cancer Res Treat.* 2010; 124:251-8.

Is there a specific magnetic resonance phenotype characteristic of hereditary breast cancer? *Tumori.* 2010; 96:363-84.

Contributions

S. Manoukian, Member of the Scientific Committee of the National Italian Network for the Surveillance of the high genetic risk women (Ministry of Health and Istituto Superiore Sanità, Rome)

S. Manoukian, Member of Italian Society of Human Genetics (S.I.G.U.) and of SIGU-Oncological Medical Genetics group



HEREDITARY DIGESTIVE TRACT TUMORS

HEAD

Lucio Bertario, MD

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RESEARCH MEMBER

Stefano Signoroni, Biol Sci D

ADMINISTRATIVES

Mariangela Di Ceglie

Ornella Galuppo

The Unit of Hereditary Digestive Tract Tumors is devoted to the counselling, molecular testing, and clinical management of individuals with genetic predisposition to the major hereditary syndromes of gastrointestinal cancer. These include Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP) and its phenotypic variant attenuated FAP, Peutz-Jeghers Syndrome, and hereditary gastric cancer. Individuals with evidence of hereditary susceptibility to cancer are counseled and informed about personal risk and that of their relatives. Depending of the fulfillment of defined criteria, individuals who receive genetic counseling are offered the possibility to undergo molecular testing for identification of specific genetic alteration(s) that may be associated with the increased risk of cancer in their families. These criteria include personal and family history of cancer, presence of specific clinical phenotypes, and tumor characteristics. The genes presently screened on a routine basis include: MLH1, MSH2, MSH6, and PMS2, cumulatively referred to as DNA mismatch repair (MMR) genes (HNPCC); APC and MUTYH (FAP and attenuated FAP); LKB1 (Peutz-Jeghers Syndrome) and CDK1 (gastric cancer). All tests are performed at the diagnostic laboratory located at IFOM (FIRC Institute of Molecular Oncology) in collaboration with the DNA Sequencing Unit of the Cogentech Consortium at the IFOM-IEO campus. During 2010, more than 500 individuals were screened for germline mutations in cancer predisposing genes. This diagnostic activity is integrated by several research programs (LILT, Rome; PIO, Bari). At the preclinical level, they are focused on the identification of genetic markers responsible for familial aggregations that test negative by the above described molecular screenings or that influence cancer risk in mutation carriers.

Keywords: colorectal cancer, familial adenomatous polyposis (FAP), Lynch syndrome (HNPCC), Peutz-Jeghers syndrome, hereditary gastric cancer

2010 RELEVANT NOTES

Collaborations

Mallorca European Group for the Hereditary Colorectal Cancer
InTEF (Network Nazionale Italiano Tumori Eredo-Famigliari)

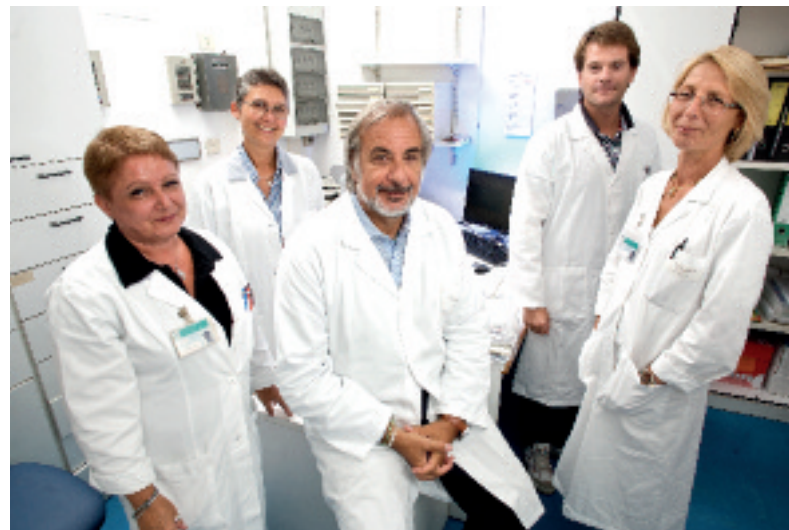
Publications

Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut*. 2010; 59:975-86.

Biomarkers in familial adenomatous polyposis: role and significance. *Front Biosci (Schol Ed)*. 2010; 2:413-21. Review

Contributions

L. Bertario, coordinator of the collaborative group for the elaboration of guidelines for clinical management of familial adenomatous polyposis, Lombardy Region



MOLECULAR BASIS OF GENETIC RISK AND GENETIC TESTING

HEAD

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Carmela Nici, Biol Sci D*

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*c/o FIRC Institute of Molecular Oncology
Foundation (IFOM)

This Unit is primarily involved in the identification and characterization of genetic elements associated with predisposition to development of cancer and its progression.

Our research aims to improve current strategies for the identification of individuals at increased risk of cancer or who are more likely to experience recurrence, due to predisposing alleles and/or somatically acquired genetic alterations. Our studies are mainly focused on breast and colorectal carcinomas, and Wilms' tumor (WT).

The major achievements during 2010 are as follows.

1. The identification of an indel polymorphism in the promoter of the CASP8 gene (rs3834129) as a modifier of breast cancer risk in carriers of BRCA1 mutations, particularly class I mutations (loss-of-function).
2. In cancer patients with double heterozygosity (DH) for mutations in both BRCA1 and BRCA2 genes, the age of disease onset was found to be comparable to that of carriers of single BRCA gene mutations; tumour development appears to be driven mainly by BRCA1 mutations.
3. The development of a procedure for the classification (in relation to cancer risk) of previously unclassified variants at splicing regions of BRCA genes, integrating in vitro and in silico analyses.
4. The identification, through reanalysis of the data from a previously performed whole-genome single nucleotide polymorphism array analysis of 77 WTs using recently developed bioinformatic tools, of different chromosomal regions associated with relapse, age at diagnosis and disease stage, as well as of focal anomalies at five regions involved in tumorigenesis and/or cancer development.
5. The identification, using transcriptome and ChIPchip arrays, of direct targets of RPF-1, a transcription factor encoded by the WT-related POU6F2 gene, and the observation that the expression of a subset of these genes, whose promoters are enriched in degenerate POU-based octamers, is directly modulated by RPF-1.

Keywords: cancer genetics, familial breast cancer, hereditary colorectal cancer, Wilms' tumor

2010 RELEVANT NOTES

Collaborations

Network Italiano Tumori Eredo-Famigliari (INTEF) - P. Radice, co-coordinator

CONsorzio degli Studi Italiani sul Tumore Ereditario alla Mammella (CONSIT TEAM) - P. Radice, coordinator

Consorzio per lo studio degli alleli MMR e dei loro modificatori (CONSAMM) P. Radice, co-coordinator

Associazione Italiana di Ematologia ed Oncologia Pediatrica (AIEOP) - D. Perotti, Wilms' tumor working group steering committee member

Fondazione Istituto FIRC di Oncologia Molecolare, Milan

IRCCS: Istituto Europeo di Oncologia and Istituto Clinico Humanitas, Milan; Istituto Nazionale dei Tumori, Fondazione Pascale, Naples and Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)

Evidence-based Network for the Interpretation of Germline Mutant Alleles (ENIGMA), P. Radice, steering committee member

Breast Cancer Consortium (BCAC)

Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA)

Colorectal cancer GENeTics (COGENT)

University of Heidelberg and University of Cologne

Centro Nacional de Investigaciones Oncológicas, Madrid and Institut Catala de Oncologia, Barcelona

University of Texas M.D. Anderson Cancer Center, Houston, Texas

Queensland Institute of Medical Research, Brisbane, Queensland

Publications

Four new cases of double heterozygosity for BRCA1 and BRCA2 gene mutations: clinical, pathological and family characteristics. *Breast Cancer Res Treat.* 2010;124:251-58.

The CASP8 rs3834129 polymorphism and breast cancer risk in BRCA1 mutation carriers. *Breast Cancer Res Treat.* 2010. [Epub ahead of print]



MOLECULAR BASIS OF GENETIC RISK, POLYGENIC MODELS

HEAD

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Angela Pettinicchio

This Unit carries out studies on the genetic epidemiology of lung cancer in humans, and is also characterizing the link between genetic susceptibility to inflammation and lung tumorigenesis in animal models.

In humans, we have identified a functional haplotype in the 5'-region of the cholinergic receptor nicotinic alpha5 (CHRNA5), on chromosomal locus 15q25, which is implicated in an increased risk of lung cancer and nicotine dependence. The functional haplotype is responsible for the modulation of the transcriptional levels of the CHRNA5 gene. We have also carried out a revision of the literature of available genome-wide association studies, showing that the identified loci exert a very small effect on the phenotype, and that most heritability remains unexplained. We have proposed that genetic heterogeneity might be involved in the complex genetics of cancer, thus implicating hundreds of genetic variants in determining cancer risk. We have also characterized the MFSD2A (major facilitator superfamily domain containing 2) gene, which maps to chromosome 1p34 within a linkage disequilibrium block containing genetic elements associated with progression of lung cancer. We found that MFSD2A expression is strongly down-regulated in lung cancer, and that exogenous expression of MFSD2A in lung cancer cells induced a G1 block, impaired adhesion and migration in vitro, and a significantly reduced tumour colony number in vitro. Overall, our data suggest that MFSD2A is a novel tumor suppressor gene in lung cancer that regulates cell cycle progression and matrix attachment. We have also carried a genome-wide linkage analysis in pedigrees of mice differing in the extent of acute inflammatory response (AIRmax or AIRmin), and determined their genetic susceptibility to lung tumorigenesis. We mapped the major inflammatory response modulator 1 locus on chromosome 7, linked to the number of infiltrating cells through the production of IL-1beta.

Keywords: genetic predisposition, SNPs, genome-wide association studies, lung cancer

2010 RELEVANT NOTES

Collaborations

Istituto Butantan, Sao Paulo

Hamon Center for Therapeutic Oncology Research, University of Texas Southwestern Medical Center, Dallas, TX

Center for Genetic Epidemiology and Modeling, Tufts Medical Center and Tufts University School of Medicine, Boston, MA

Stazione Zoologica Anton Dohrn, Naples

Publications

Promoter polymorphisms and transcript levels of nicotinic receptor CHRNA5. *J Natl Cancer Inst.* 2010; 102:1366-70.

Beyond genome-wide association studies: genetic heterogeneity and individual predisposition to cancer. *Trends Genet.* 2010; 26:132-41.

