The main aim of the U900 Cancer Epidemiology team is to study the genetic factors likely to play a part in the etiology of cancer. Taking into account all known (or expected) risk factors, we examine the interactions between these factors, aided by advances in the techniques of molecular genetics. These studies are of increasing value in complex diseases such as cancer, as most of the genes identified have incomplete penetrance. Our aim is to improve estimates of the effects of risk factors and individual risks, and hence to improve screening and follow-up strategies.

Environment-lifestyle gene interactions in the etiology of breast cancer: GENECAN, GENEPSO and IBCCS studies

The identification of the BRCA1 and BRCA2 genes was a great advance in understanding predisposition to breast cancer. However, there are several biological and epidemiological arguments suggesting that environment/lifestyle factors and particularly gynecological-obstetric factors can modify the risk of cancer associated with the BRCA1 and BRCA2 genes. Our team is studying the effect of these factors on genetic risk through three multicenter studies: GENECAN, GENEPSO and IBCCS.

- **GENECAN** is a familial, multicenter, national study in which the families were recruited by cancer geneticists of the Genetic and Cancer Group (GGC) of the National federation of french cancer centers.
- **GENEPSO**, a national cohort of carriers of BRCA mutations, was initiated in 2000 and coordinated by the René-Huguenin Center (St Cloud), and involves all the consultations of the GGC.

The GENEPSO study is also a major component of the international project IBCCS, which involves several, mostly European, centers. A total of 3580 subjects have so far been recruited for the IBCCS study, 26% of them from the GENEPSO study. Our team is a member of the international analytical group IBCCS, which analyzes data and develops methods needed for these analyses. The first results concerned the risks associated with reproductive factors, exposure to radiation, and use of oral contraceptives.
CoF_AT study of the risk of cancer in the parents of children with ataxia-telangiectasia

Ataxia-telangiectasia (AT) is a rare childhood disease characterized by severe immune deficiency and progressive motor handicap due to degeneration of cerebellar neurons. AT is also associated with a high risk of cancer (35% at the age of 20 years). Mothers of affected children seem to have a very high risk of breast cancer. Despite the low prevalence of AT, the frequency of AT heterozygotes (hetAT) in the general population can reach 1%. And the risk of developing breast cancer associated with heterozygosity affects a large number of women (150 000 to 300 000 in France).

This is why our team has set up a prospective cohort of women related to a child with AT:

- to offer early breast cancer screening to women heterozygous and not heterozygous for AT.
- to estimate the cancer risk, study the role of modifying factors, and establish a collection of blood samples and tumor tissue specimens.

The women are included and followed up by means of nationwide oncogenetic and genetic consultations. The Institut Curie cancer genetics Department screens for mutations. The project has been funded since 2005 by the Fondation de France, EDF and the Ligue nationale contre le cancer.

Identification and characterization of new breast cancer predisposition genes: GENESIS study

Among the familial forms of breast cancer that prompt a molecular study of the BRCA1 and BRCA2 genes, only 20% have a mutation. Our team coordinates the GENESIS study (GENE SiSter) in collaboration with D. Stoppa-Lyonnet (genetic oncology, Institut Curie) et O. Sinilnikova (Hospices Civils, Centre Léon Bérard) with a view to identifying new predisposition genes by the study of pairs of affected sisters and their controls: disease-free sisters and relatives through marriage. People are recruited by the GGC. The methodological approach is double : Linkage and association analyses. To minimize loss of power caused by a probable genetic heterogeneity, we stratify the analyses by endophenotypes (breast density, tumor characteristics, radiosensitivity, …).

The national study started in April 2007 and 1467 people had been included by March 2008. This project should constitute an important advance in understanding of the excess familial risk of breast cancer. The project has been funded since 2006 by the Ligue nationale contre le cancer and Inca.
Evaluation and development of strategies for the study of gene-environment interactions

Our studies on gene-environment interactions soon reached their limits: methodological problems such as loss of power, interpretation of results because of the multiplicity of statistical tests done, and missing data, which can be very frequent in familial studies. This is why the Epidemiology Team plans to evaluate existing strategies and to develop new approaches to improve the detection of these interactions.

Key publications

Year of publication 2014

Rare mutations in RINT1 predispose carriers to breast and Lynch syndrome-spectrum cancers.
Cancer discovery : 804-15 : DOI : 10.1158/2159-8290.CD-14-0212

Year of publication 2013

Rare key functional domain missense substitutions in MRE11A, RAD50, and NBN contribute to breast cancer susceptibility: results from a Breast Cancer Family Registry case-control mutation-screening study.
Breast cancer research : BCR : R58 : DOI : 10.1186/bcr3669

Elena Bonora, Cosmeri Rizzato, Chiara Diquigiovanni, Tiphaine Oudot-Mellakh, Daniele Campa, Manuela Vargioli, Mickaël Guedj, , James D McKay, Giovanni Romeo, Federico Canzian, Fabienne Lesueur (2013 Apr 29)
The FOXE1 locus is a major genetic determinant for familial nonmedullary
thyroid carcinoma.

**Year of publication 2012**


**Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: retrospective cohort study (GENE-RAD-RISK).**
*Bmj (Clinical research ed.)* : e5660 : [DOI: 10.1136/bmj.e5660]

Julie Lecarpentier, Catherine Noguès, Emmanuelle Mouret-Fourme, Marion Gauthier-Villars, Christine Lasset, Jean-Pierre Fricker, Olivier Caron, Dominique Stoppa-Lyonnet, Pascaline Berthet, Laurence Faivre, Valérie Bonadona, Bruno Buecher, Isabelle Coupier, Laurence Gladieux, Paul Gesta, François Eisinger, Marc Frénay, Elisabeth Luporsi, Alain Lortholary, Chrystelle Colas, Catherine Dugast, Michel Longy, Pascal Pujol, Julie Tinat, , Rosette Lidereau, Nadine Andrieu (2012 Feb 22)

**Variation in breast cancer risk associated with factors related to pregnancies according to truncating mutation location, in the French National BRCA1 and BRCA2 mutations carrier cohort (GENEPSO).**