Title

The Cancer Genetics Network: Recruitment Results and Pilot Studies

Journal

Public Health Genomics, 6(3)

ISSN

1662-4246

Authors

Anton-Culver, Hoda

Ziogas, Argyrios

Bowen, Deborah

et al.

Publication Date

2003

DOI

10.1159/000078165

Original Paper

Community Genetics

Community Genet 2003;6:171–177
DOI: 10.1159/000078165

The Cancer Genetics Network: Recruitment Results and Pilot Studies

Hoda Anton-Culver[a] Argyrios Ziogas[a] Deborah Bowen[b]
Dianne Finkelstein[c] Constance Griffin[d] James Hanson[e] Claudine Isaacs[f]
Carol Kasten-Sportes[e] Geraldine Mineau[g] Prakash Nadkarni[h]
Barbara Rimer[e] Joellen Schildkraut[i] Louise Strong[j] Barbara Weber[k]
Deborah Winn[e] Robert Hiatt[e] Susan Nayfield[e]

[a]Epidemiology Division, College of Medicine, University of California, Irvine, Calif., [b]Fred Hutchinson Cancer Research Center, Seattle, Wash., [c]Biostatistics Cancer Center, Massachusetts General Hospital, Boston, Mass., [d]Department of Pathology, Oncology and Medicine, Johns Hopkins University, Baltimore, Md., [e]Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Md., [f]Lombardi Cancer Center, Georgetown University, Washington, D.C., [g]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah, [h]Center for Medical Informatics, Yale University Medical School, New Haven, Conn., [i]Duke Cancer Center, Duke University Medical School, Durham, N.C., [j]MD Anderson Cancer Center, University of Texas, Houston, Tex., and [k]Cancer Center, University of Pennsylvania, Philadelphia, Pa., USA

Key Words
Cancer genetics · Cancer risk · Genetic testing · Screening trials · Translational research

Abstract
Objective: The National Cancer Institute established the Cancer Genetics Network (CGN) to support collaborative investigations into the genetic basis of cancer susceptibility, explore mechanisms to integrate this new knowledge into medical practice, and identify ways of addressing the associated psychosocial, ethical, legal, and public health issues. ***Subjects and Methods:*** The CGN has developed the complex infrastructure required to support the projects, including the establishment of guidelines and policies, uniform methods, standard questionnaires to be used by all of the centers, and a standard format for submission of data to the Informatics Center. Cancer patients and their family members have been invited to enroll and be included in a pool of potential study participants. The Information Technology Group is responsible for support of the design, implementation, and maintenance of the multicenter Network-wide research protocols. ***Results:*** As of January 2004, the CGN contained data on 23,995 probands (participants) and 425,798 family members. As a resource for cancer genetic studies, the CGN has a large number of probands and first-degree relatives with and without cancer and with multiple ethnicities. Different study designs can be used including case-control, case-case, and family studies. ***Conclusions:*** The unique resources of the CGN are available for studies on cancer genetic susceptibility, translational research, and behavioral research. The CGN is now at a point where approved collaborators may have access to enrolled patients and their families for special studies, as well as to the clinical, environmental and family cancer history data banked in the Informatics Center.

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1422–2795/03/0063–0171$19.50/0

Accessible online at:
www.karger.com/cmg

Hoda Anton-Culver, PhD
Epidemiology Division, College of Medicine
224 Irvine Hall, University of California
Irvine, CA 92697-7550 (USA)
Tel. +1 949 824 7416, Fax +1 949 824 4773, E-Mail hantoncu@uci.edu

Introduction

The National Cancer Institute (NCI) established the Cancer Genetics Network (CGN) to support collaborative investigations into the genetic basis of cancer susceptibility, explore mechanisms to integrate this new knowledge into medical practice, and identify ways of addressing the associated psychosocial, ethical, legal, and public health issues. As of January 2004, the CGN contained data on 23,995 probands (participants) and 425,798 family members. The CGN includes probands with all cancer sites. Prostate cancer (n = 3,427) among males and breast cancer (n = 6,551) among females are the most common sites. A large proportion of CGN probands have familial cancers, including 3,663 familial breast cancer, 1,819 familial ovarian cancer, 1,268 familial prostate cancer, and 706 familial colorectal cancers. The CGN participants include White/Caucasian non-Ashkenazi (79%), Ashkenazi (7%), Hispanic (5%), Black (5%), Asian (2%), and other ethnicities (2%). The CGN is now a rich resource for collaborative studies on cancer genetic susceptibility, translational research, and behavioral research. This resource is available to approved researchers and can provide clinical, environmental, and family cancer history data on CGN enrollees and access to the patients and their families for research studies, including the required biological specimens.

Advances in human genetics have provided an important new opportunity to identify cancer genes through studies of cancer-prone families and individuals with no family history of cancer [1, 2]. In 1998, NCI funded an innovative national CGN to provide participating researchers access to a breadth of research data, potential study participants, and human tissue samples not currently available to most individual cancer genetics programs. Participation in the network and its accompanying Informatics and Information Technology infrastructure was through cooperative agreements with research institutions that submitted proposals in 1997, and competed for funding through the National Institutes of Health peer-review process [3, 4].

Some of the pressing questions that the network addresses are: How common are the genetic variations that cause different cancers in different population groups? What determines whether someone with a genetic change gets cancer and what are the possible modifiers of risk? What environmental exposures may interact with genetic susceptibility to alter cancer risk? How can genetic discoveries be translated into ways to prevent, early detect, and better treat cancer? What ethical, psychological, social, and family issues affect healthy individuals and their families who carry cancer susceptibility gene mutations?

Methods

Building the Infrastructure

The first year of the CGN was spent developing the complex infrastructure required to support the projects. This included the establishment of guidelines and policies, uniform methods, standard questionnaires to be used by all of the centers, and a standard format for submission of data to the Informatics Center (IC). The network then began to invite cancer patients and their family members to enroll and be included in a pool of potential study participants. Special attention was paid to underserved and unique populations. Genetic testing and biospecimen collection were not required for enrollment in the network, but may be part of participation in special studies. Stringent privacy safeguards ensure that participation in the network, and in any studies conducted through it, is confidential.

When special research studies are initiated, a pool of interested individuals can be quickly assembled and be invited to participate. The identification of subjects from the individual network centers makes it possible to have sufficient numbers of study participants to answer significant questions definitively. The CGN has the ability to enroll populations with rare cancers with the collection of required biospecimens. The network also facilitates the exchange of information on cancer genetics and research resources within the larger cancer and cancer genetics communities. The centers provide broad access to information about genetic services and educational materials for use by researchers, health care professionals, and the public. Additionally, NCI funding for the network supports pilot studies on cancer genetics, fostering collaborative research among the participating institutions, and between them and researchers outside the network. The CGN actively encourages optimal use of this unique national resource.

Recruitment of Subjects

There are four population-based and four clinic-based centers (table 1). The centers with population-based cancer registries use them to contact and enroll patients and their family members. Methods of case ascertainment and recruitment of study subjects have been established to achieve the highest possible participation rate. Subjects ascertained and agreeing to participate are then interviewed regarding their family history of cancer. The participation rate in the population-based cancer registry centers is commonly between 70 and 90% and for clinic-based is 45–90%. Detailed family history information on up to four generations is obtained through mailed questionnaires and telephone interviews. Interviewers include those who speak Spanish, Vietnamese, Chinese, and several other languages. Relatives are enumerated by date of birth, gender, vital status, type of cancer, date of diagnosis, and date of death, if applicable. In special studies, food frequency questionnaires, psychosocial questionnaires, and epidemiologic risk factor questionnaires are used. Follow-up of probands is done annually and changes in cancer status for probands and their family members are noted and tracked. As of January 2004, 12,479 probands completed the annual follow-up questionnaire, 789 were deceased, 166 declined further participa-

Table 1. Ascertainment mode by center

Center name	Population based		Clinic based		Referral	
	%	n	%	n	%	n
Carolina-Georgia	46	960	36	755	18	378
Georgetown	1	8	96	1,221	3	40
Mid-Atlantic	N/A	N/A	100	1,223	N/A	N/A
Northwest	82	2,913	N/A	N/A	18	648
Texas	5	80	86	1,327	9	143
University of Penn.	4	50	96	1,291	0	3
Rocky Mountain	96	9,193	0	6	4	384
UCI-UCSD	77	1,822	0	5	23	529
Total	66	15,026	25	5,828	9	2,125

Nine records are not included due to missing ascertainment mode. UCI-UCSD = University of California, Irvine/San Diego; N/A = not applicable.

tion, 381 were lost to follow-up, and 53 were not participating for other reasons.

In the clinic-based centers, physicians and other health care professionals directly refer patients to CGN Centers. The participation rate in the clinic-based centers is 45–90%. The same family history interview is followed by additional questionnaires in special studies. Other participants are self-referred through community awareness and education efforts and CGN Center and NCI websites. All investigations involving human subjects were performed after approval by a local institutional review board and in accord with an assurance filed with and approved by the US Department of Health and Human Services.

Information Technology Group

The Information Technology Group (ITG) is responsible for the development of the informatics infrastructure necessary to perform the investigations within the CGN. The group is responsible for support of the design, implementation, and maintenance of the multicenter Network-wide research protocols. The group also develops information systems that facilitate the exchange of human cancer genetics information and resources within the larger cancer genetics community. This includes electronic mechanisms to broaden public health professional access to genetic services and educational material, the establishment of a clearinghouse of human cancer genetics resources and the development of means to extend access to and connections among researchers, service providers, and the general public.

Informatics Center at the University of California at Irvine

Development of Questionnaires, Data Standards, Guidelines, and Protocols. With the inception of funding in August 1998, the CGN Informatics Center at the University of California at Irvine began the process of developing draft data standards.

Special Studies Database at Yale

TrialDB is a Web-accessible database developed at the Yale Center for Medical Informatics, primarily through NCI and National Center for Research Resources support. It serves to store data on pilot studies conducted by CGN investigators. TrialDB is a *generic* clinical study database.

Statistical Coordinating Center at MGH

The Statistical Coordinating Center at the Massachusetts General Hospital collaborates with Yale on implementing and modifying the TrialDB database to be utilized in studies conducted by the CGN. The Statistical Coordinating Center is involved at all stages of study design and management.

Education and Technical Support

CGN steering and working group committee meetings are held every 6 months at one of the centers on a rotating basis. Educational and scientific presentations and workshops are included in these meetings as needed. Working groups include: the Behavioral Science Working Group, the Translational Working Group, the Bioethics Working Group, the Education and Communication Working Group, the Biospecimen Working Group, and the ITG Working Group.

Steering Committee and Advisory Committee

The Steering Committee serves as the main governing board of the Network and is responsible for the design and execution of Network-wide research protocols and the assembly of the study populations required for their conduct. Its membership includes the principal investigators of the Centers, the NCI Program Coordinator, directors of other coordinating groups, and patient advocates.

The Advisory Committee is composed of senior scientists with interdisciplinary expertise in cancer genetics research. Members are nominated by the Steering Committee members and are appointed by NCI for a 2-year tenure.

Table 2. Ascertainment mode by ethnicity

Ethnicity	Population based		Clinic based		Referral		Total	
	%	n	%	n	%	n	%	n
White, non-Ashkenazi	84	12,618	66	3,875	76	1,619	79	18,112
Ashkenazi	3	375	18	1,045	8	165	7	1,585
Black	3	436	10	563	5	99	5	1,098
Asian/Pacific Islander	3	500	1	56	2	37	2	593
Hispanic	5	774	3	186	7	149	5	1,109
Other	2	320	2	96	2	53	2	469
Total	66	15,023	25	5,821	9	2,122	100	22,966

Twenty-two records are not included due to missing ascertainment mode.

Table 3. Cancer status by ethnicity

	Probands without cancer		Probands with one cancer		Probands with two or more cancers		Total	
	%	n	%	n	%	n	%	n
White, non-Ashkenazi	78	6,187	78	9,317	83	2,612	79	18,116
Ashkenazi	9	667	6	676	8	242	7	1,585
Black	5	387	5	640	2	72	5	1,099
Asian/Pacific Islander	1	101	4	442	2	52	2	595
Hispanic	5	419	5	586	3	105	5	1,110
Other	2	175	2	241	2	53	2	469
Total	35	7,936	52	11,902	14	3,136	100	22,974

Fourteen records are not included due to missing ethnicity.

Results

As of January 2004, the CGN contained data on 23,995 probands (participants) and 425,798 family members. Of the 23,995 probands in the CGN Core, 1,007 were participating in pilot studies only and were excluded from the results. The CGN participants include all ethnicities: White/Caucasian non-Ashkenazi (79%), Ashkenazi (7%), Hispanic (5%), Black (5%), Asian (2%), and other ethnicities (2%). Description of participants by recruitment mode, whether by population-based cancer registries, high-risk clinics, or by self, physician, support group or family member referral are seen in table 1. The majority of CGN participants were recruited from population-based cancer registries (table 2). However, for Black and Ashkenazi participants, a greater number were recruited from high-risk clinics (51 and 66%, respectively). Table 3 shows the number of probands by ethnicity and cancer status. Different study designs can be used including case-control, case-case, and family studies. Tables 4 and 5 list the major cancer sites of CGN participants by sex and ethnicity. Prostate cancer (n = 3,427) and non-melanoma skin cancer (n = 928) were the two most common sites among males, while breast cancer (n = 6,551) and non-melanoma skin cancer (n = 1,138) were the most common sites among females. The data also show that the CGN has data on both common and uncommon cancers. Furthermore, 7,936 CGN participants did not have a personal history of cancer.

Table 4. Number of probands by tumor type and sex (some probands may have multiple tumors)

Cancer type	Male	Female	Total
Breast	55	6,551	6,606
Prostate	3,427	–	3,427
Non-melanoma skin	928	1,138	2,066
Colorectal	790	833	1,623
Melanoma	274	359	633
Ovary	–	648	648
Thyroid	100	424	524
Lymph nodes	166	224	390
Lung	134	178	312
Uterine	–	242	242
Bladder	140	42	182
Pancreas	65	58	123
Cervix	–	186	186
Kidney	101	100	201
Buccal	33	45	78
Bone marrow	31	24	55
Brain	18	27	45
Liver	32	27	59
Testis	31	–	31
Bone	13	29	42
Stomach	17	7	24
Eye orbit	9	16	25
Esophagus	11	4	15
Larynx	13	2	15
Soft tissue	6	9	15
Other female	–	15	15
Vulva	–	14	14
Small intestine	5	8	13
Vagina	–	8	8
Other urinary	5	3	8
Endocrine	3	6	9
Peritoneum	1	8	9
Anus	3	3	6
CNS	1	7	8
Other biliary	1	4	5
Nasal	3	1	4
Ureter	2	2	4
Gallbladder	–	3	3
Penis	1	–	1
Other	50	76	126

A large number of first-degree relatives of CGN participants have also been reported to have had cancer. Table 6 presents the cancer distribution of first-degree relatives of prostate, colorectal, and breast cancer probands. There were also a large number of first-degree relatives without a history of cancer. Many of the probands in the CGN have familial or apparent hereditary cancers (table 7). Most notably, there were 3,663 probands with familial breast cancer and 1,819 probands with familial ovarian cancer. There were also 1,268 probands with familial prostate cancers, and 706 familial colorectal cancers. Table 8 further details the number of proband-sibling pairs affected with the same cancer as reported by CGN probands.

Discussion

The resources of the CGN described above are available for studies on cancer genetic susceptibility, translational research, and behavioral research. The CGN investigators and co-investigators at the eight CGN Centers have already begun collaborations with the CGN on several fronts. The following special studies are underway:

Ovarian Cancer Screening Study: test two approaches to screening for ovarian cancer among women at high risk for the disease using a blood test for CA 125 and transvaginal ultrasound. This particular study has demonstrated the CGN's ability to collect and track large numbers of biospecimens from multiple sites. The Gynecologic Oncology Group and the Ovarian Specialized Programs of Research Excellence sites are also collaborating with the CGN on this pilot.

Study of Inheritance of Colon Cancer among Sibling Pairs: search for novel colon cancer susceptibility loci among sibling pairs who have a history of colon cancer. The Cancer Family Registry for Colon Studies is collaborating on this special study.

Recruitment of Families with Prostate Cancer: obtain, characterize, and document biological specimens obtained from families who have a history of onset of prostate cancer at an early age.

Genetic and Environmental Modifiers of Cancer Risk among Women with BRCA1 and BRCA2 Mutations: study genetic and environmental factors that may modify the risk for developing breast and ovarian cancer among women who are carriers of BRCA1 and 2 mutations.

Comparison of Models to Estimate a Woman's Risk of Being a BRCA1 or BRCA2 Carrier: compare statistical models for estimating the risk of a woman being a BRCA1 or BRCA2 mutation carrier based on her family history.

Factors Affecting Participation Rates in the CGN: conduct a prospective randomized trial to evaluate the impact of enrollment incentives on participation in the CGN.

Breast Screening Study: obtain pilot data on the benefits of various breast cancer screening techniques, including MRI, high-resolution ultrasound, and mammography

Table 5. Number of probands by tumor type and ethnicity (some probands may have multiple tumors)

Cancer type	White Ashkenazi	White, non-Ashkenazi	Black	Asian/Pacific Islander	Hispanic	Other
Breast	554	4,894	463	223	356	115
Prostate	112	2,887	140	73	151	64
Non-melanoma skin	123	1,878	9	6	15	35
Colorectal	47	1,315	36	91	100	32
Melanoma	53	564	2	0	4	10
Ovary	56	506	27	13	31	14
Thyroid	40	427	5	16	17	19
Lymph nodes	31	313	6	8	24	8
Lung	18	246	5	32	6	5
Uterus	9	208	4	8	9	3
Bladder	15	151	3	2	7	4
Other	55	908	50	57	50	27
Total	1,113	14,297	750	529	770	336

Table 6. Distribution of tumors by type among first-degree relatives (FDR) of probands with prostate, colorectal, and breast cancer

Cancer type in FDR of probands	FDR (n = 46,569) of breast cancer probands (n = 6,606)	FDR (n = 27,710) of prostate cancer probands (n = 3,427)	FDR (n = 12,935) of colorectal cancer probands (n = 1,623)
No cancer	37,875	22,884	10,737
Breast	3,039	712	342
Prostate	921	1,468	252
Colorectal	846	529	521
Lung	711	427	193
Non-melanoma skin	676	284	139
Ovary	434	101	61
Lymph nodes	353	223	115
Melanoma	279	100	69
Uterus	260	100	73
Stomach	208	141	72
Pancreas	181	94	53
Buccal	167	93	53
Cervix	170	54	37
Bone marrow	166	114	53
Bladder	171	79	36
Brain	165	90	53
Liver	135	125	52
Kidney	110	55	39
Bone	101	70	36
Thyroid	96	34	25
Esophagus	87	31	17
Testis	39	29	19
Larynx	35	16	2
Gallbladder	18	7	6
Other	397	297	137
Total FDR with cancer[a]	8,694	4,826	2,198

[a] Some FDR may have multiple tumors.

Table 7. Number of families with familial versus non-familial cancers

Cancer type	Familial[a]	Non-familial[b]
Colorectal	706	3,613
Breast[c]	3,663	6,579
Ovary[c]	1,819	4,927
Prostate	1,268	3,046
Melanoma	155	1,163
Non-melanoma skin	821	2,786
Lung	240	2,048

[a] Proband and at least 1 first-degree relative (FDR) diagnosed with the same cancer *or*, if proband is unaffected, at least 2 FDR diagnosed with the same cancer.
[b] Proband has no FDR diagnosed with the same cancer, *or*, if proband is unaffected, only 1 FDR diagnosed with specific cancer.
[c] Female FDR can have breast and/or ovarian cancer to be considered familial.

Table 8. Number of proband-sibling pairs affected with the same cancer

Cancer type	n
Breast	1,350
Prostate	804
Non-melanoma skin	322
Colorectal	231
Melanoma	50
Lung	48
Lymph nodes	13
Thyroid	12
Ovary	18
Uterine	13
Cervix	10
Kidney	10
Pancreas	4
Bone marrow	4
Bladder	2

in women at genetically high risk for breast cancer. This study is a collaborative effort between the CGN and the International Breast MRI Consortium.

The primary strengths of the CGN include the fact that it is a core registry of approximately 24,000 probands; it is more comprehensive than other registries in that it deals with multiple cancers rather than concentrating on one (such as the prostate, breast or colon registries); it carries out annual follow-up; it has developed methods for collecting biospecimens, and it has a statistical coordinating center. As for weaknesses, the CGN is not able to represent the high-mortality cancers, and it does not have initial biospecimens on all of its probands.

The CGN is now at a point where approved collaborators may have access to enrolled patients and their families for special studies, as well as to the clinical, environmental, and family cancer history data banked in the Informatics Center. Interested members of the public who wish to enroll in the CGN will find further information on the Center closest to them, and the special studies that they may be interested in, at the CGN website (http://epi.grants.cancer.gov/CGN/enrollment.html).

Prospective investigators may obtain information on collaborative studies at the CGN website (http://epi.grants.cancer.gov/CGN/prospective.html). Investigators who are interested in accessing the data or including registry enrollees in ongoing or proposed studies should prepare a 1-page description of their research to include the specific aims and an explanation of the role of CGN enrollees in the research. Proposals and inquiries should be directed to Carol Kasten-Sportes, MD, Epidemiology and Genetics Research Program, Division of Cancer Control and Population Sciences, NCI, by phone at +1 301 402 8212 or by e-mail: kastenca@ail.nih.gov.

References

1 Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al: The sequence of the human genome. Science 2001;291:1304–1351.
2 Lander ES, Linton LM, Birren B: Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.
3 National Cancer Institute Request for Application (RFA). Cancer Genetics Network, 1997. http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-97_004.html.
4 National Cancer Institute Request for Application (RFA). Cancer Genetics Network Informatics and Information Technology Group, 1997. http://grants.nih.gov/grants/guide/rfa-files/rfa-ca-97_019.html.