



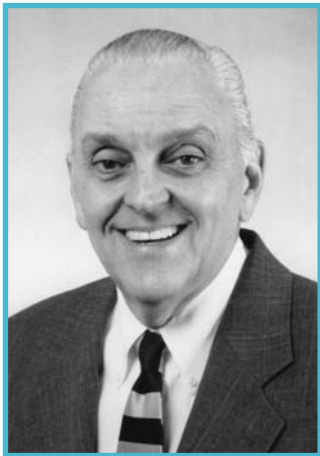
# Gilda Radner

year anniversary!

# 25

## Familial Ovarian Cancer Registry

## How It All Began...



Dr. Steven Piver, MD  
 Founder & Director Gilda Radner  
 Familial Ovarian Cancer Registry

In 2006, the Gilda Radner Familial Ovarian Cancer Registry celebrates its 25-year anniversary. During these 25 years the Registry has had thousands of women with ovarian cancer either personally or in their family complete detailed forms on their medical history and data of their extended family. Data from these forms, coupled with medical records and biosamples, have afforded members of the Registry and collaborating scientists the opportunity to study familial or hereditary ovarian cancer. In addition, thousands of women have

contacted the Registry seeking answers to worrisome questions either about themselves or their loved ones.

Today it not unusual to learn that 5-10% of epithelial ovarian cancers are caused by mutations in BRCA1 and BRCA2. But these two genes were only cloned in 1994 and 1995, respectively, and the fact that ovarian cancer could be inherited from one's mother or father by a mutated gene was unknown in the 1970s. There were rare case reports of familial ovarian cancer, a term to describe clustering of epithelial ovarian cancers in families commonly but incorrectly used to mean genetic. So, when in 1977, a family came under our care with five members with epithelial ovarian cancer spanning three generations, this family was reported in Gynecologic Oncology as an unusual case report. Prior to that case report only four families with epithelial ovarian cancer spanning three generations had been reported. Then, to our surprise, in 1978, a second family came under our care in which three sisters, their first cousin and their first cousin's daughter all had epithelial ovarian cancer. A review of the English literature on "familial" ovarian cancer demonstrated

that during the 40-year period, 1929-1969, there had been only five families reported in which epithelial ovarian cancer occurred in multiple close relatives, whereas in the 1970s an additional 26 families with familial ovarian cancer were reported. Our initial thought was that some environmental factor resulted in the near exponential increase in reported cases of familial ovarian cancer in the decade of the 1970s compared to the four previous decades.

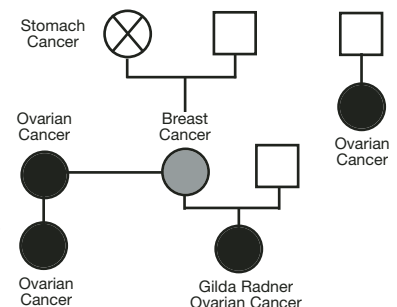
Therefore, in 1981 the Familial Ovarian Cancer Registry was initiated at Roswell Park Cancer Institute in an attempt to document the number of cases occurring in the United States and to study possible environmental factors that could account for the sudden rise in reported cases in the 1970s. Advertisements were placed in medical journals, and letters concerning the Registry were sent to departments of Obstetrics and Gynecology in the United States. In addition, New York State cases of familial ovarian cancer were identified by the New York State Department of Health, Bureau of Cancer Control. By 1983, the Registry had enrolled 94 families consisting of 201 cases in which multiple first degree relatives were affected by ovarian cancer, which was significantly more than the first 46 cases reported in the English literature up to that time. However, it became apparent that many of the Registry members with familial ovarian cancer were diagnosed during the 1950s and 1960s, indicating that this condition was not a new entity but rather seldom previously documented. Although 76 families were enrolled in the first year, enrollment fell off precip-

## A Message from Gene Wilder

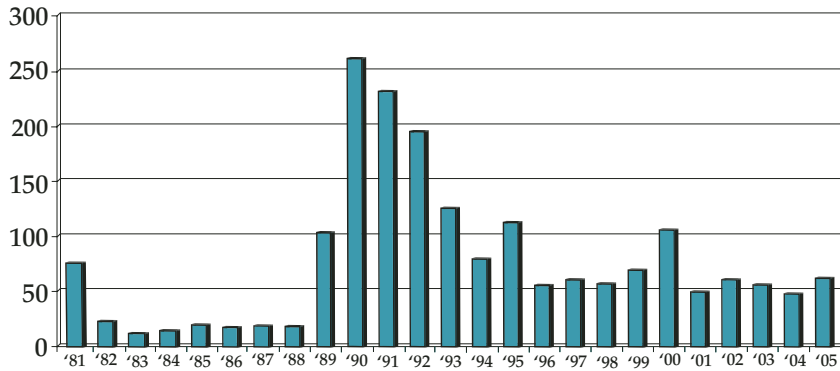
"I have met people who said, *It was something I did and God is punishing me for it; and others who have said, Why me? I have done nothing!* In both cases, they were saying the same thing: that God brought on their cancer. Well, we believe what we believe and superstition is universal. I can't make anyone changes his or her beliefs - I just wish I could. This is what I believe: It is not God who gave you cancer, it is not because you needed cancer to learn some lesson; and it is not because of your past life or your future life - it is because of genetics and environment!"

There is one if that I am sure of: If Gilda had known of the family link in ovarian cancer, she would have pursued Dr. Piver like Stanley pursued Dr. Livingstone. I am grateful that I have found him at all, so that I can help him find other Gildas and pull them out of the woods."

Gilda's Family pedigree illustrates her family history of ovarian cancer (●), and breast (●). In past generations, ovarian cancer might have been known as "stomach" cancer.



### The Gilda Radner Familial Ovarian Cancer Registry



From 1981 to 2005 the Registry, renamed in Gilda Radner's Honor in 1989, has enrolled 1870 families with two or more close relatives with ovarian cancer.

itously with only 11-23 families being enrolled per year from 1982 to 1988. In 1989, the great comedic actress Gilda Radner died of ovarian cancer. A report on Gilda Radner's death from ovarian cancer in the May 30, 1989 edition of the Washington Post entitled "Fighting Ovarian Cancer: Doctors Don't Know Who Is at Risk or Why" stated that "Genetics

could play a role in a very small number of cases. At Roswell Park Cancer Institute in Buffalo, NY, M. Steven Piver has collected a national registry of 200 ovarian cancer families, where the disease reappears in each generation.....For more information on the Familial Ovarian Cancer Registry, write M. Steven Piver, MD, Roswell Park Cancer Institute, Buffalo NY 14263." With the unanticipated media attention in the two years after the death of Gilda Radner from ovarian cancer, the Registry enrolled 450 families with familial ovarian cancer. The Registry was renamed in honor of Gilda Radner, the Gilda Radner Familial Ovarian Cancer Registry (GRFOCR). Gilda Radner's husband, Gene Wilder, became the Honorary Chair of the Registry. In 1996, Dr. Piver and Mr. Wilder published their book, *Gilda's Disease: Sharing Personal Experiences and a Medical Perspective on Ovarian Cancer*. Through the year 2005, the Registry has enrolled 1870 families with two or more first or second degree relatives with epithelial ovarian cancer with information on approximately 35,000 family members.

## Registry Research:

*then and now*



A major goal of the Registry is to identify inherited mutations in genes that predispose women to develop inherited ovarian cancer. In 1994, Registry resources assisted in identifying the link between the BRCA1 gene and inherited predisposition to develop ovarian cancer. Also, Registry research has made important contributions in classifying sub-types of ovarian cancer that occur in BRCA1 and BRCA2 mutation carriers.

Corporation, and with researchers at Roswell Park Cancer Institute and the State University of New York at Buffalo to determine if inherited mutations in other genes are responsible for disease in the families without BRCA1 or BRCA2 mutations.

Additionally, this year we anticipate screening for BRCA1 and BRCA2 mutations in 64 families who have not yet been tested.

Moreover, the Registry has awarded Dr. Ping Liang, a researcher at Roswell Park Cancer Institute, a start-up grant of \$30,000 for a research project designed to develop technical improvements in the detection of BRCA1 and BRCA2 mutations over current methods. It is hoped that these research initiatives will lead to discovery of new ways to reduce risk for developing ovarian cancer in women with an inherited predisposition.

1. Oral Contraceptive Use and Ovarian Cancer Risk Among Carriers of BRCA1 or BRCA2 Mutations. AS Whittemore, RR Balise, PDP Pharoah, RA DiCioccio, Kathleen Cuninghnam Foundation Consortium for Research into Familial Breast Cancer (kConFAB), I Oakley-Girvan, SJ Ramus, M Daly, MB Usinowicz, K Garlinghouse-Jones, BAJ Ponder, S Buys, R Senie, I Andulis, E John, JL Hopper, MS Piver. *British Journal of Cancer* (2004), 1-5. [www.bjcancer.com](http://www.bjcancer.com)

In 2004, the Registry published research indicating an association between reduced ovarian cancer risk and oral contraceptive use in BRCA1 and BRCA2 mutation carriers(1).

This year we anticipate publication of our screening of 137 Registry enrolled families for inherited mutations in BRCA1 or BRCA2 genes. Mutations were found in 52 families but 85 families did not have mutations in either gene. This means 62% of Registry families with multiple cases of ovarian cancer are not explained by mutations in BRCA1 and BRCA2 genes.

We have initiated three separate research collaborations with the National Cancer Institute, with Myriad Genetics

Be Aware or as our friends in the National Ovarian Cancer Alliance say...

“Until there’s a test, awareness is best.”

### Risk Factors for Ovarian Cancer

- High fat diet
- Never having children
- Infertility, or not having children till late in life
- Using infertility drugs, but not becoming pregnant
- Starting your periods at a young age, or going through menopause at an older than average age
- Use of talcum powder on genital area
- Caucasian race
- Being of Jewish descent
- Family or personal history of ovarian, breast or colon cancer

Of these risk factors, the most significant is a family history of ovarian and/or breast cancer. Having one close relative with ovarian cancer increases a woman’s risk of developing ovarian cancer by nearly three times. (A woman without a family history of ovarian or breast cancer has a 1.8% chance of developing ovarian cancer, so a woman with one family member has a nearly 7% chance of developing ovarian cancer). Having additional members with ovarian or breast cancer increases the risk even further. It is important to know your family medical history.

Fortunately, there are a number of factors that are associated with a lower risk of ovarian cancer.

- Use of birth control pills
- Having multiple children
- Breast feeding
- Tubal ligation
- Prophylactic oophorectomy (removal of the ovaries and fallopian tubes)

It is important to understand most women with risk factors for ovarian cancer will never actually develop ovarian cancer. Similarly, most women with ovarian cancer do not have any strong risk factors for the disease. Even with significant risk factors such as family history, the overall chances of getting ovarian cancer are still small.

#### Registry member Marolyn Wingard’s comment:

“In 2003, at the age of 67, after more than a year of indigestion, bladder problems, much gas, and bowel changes, I saw a newspaper article in which an ovarian cancer survivor described her symptoms prior to her surgery. She, a nurse, had been complaining of symptoms for some time. I showed this article to my family physician, told him I had these symptoms and he ordered a transvaginal ultrasound, that was inconclusive, followed by a CAT scan, also inconclusive, showing a VERY small unidentified mass. The gynecologist I saw did not think it was cancer, told me not to worry and come back for a recheck in six months. Six months later (2004) the CAT scan showed the mass had doubled (they still did not think it was cancer), but surgery showed Stage III ovarian cancer — I have had a hysterectomy and bilateral salpingo oophorectomy (removal of the ovaries and fallopian tubes) and nine months of chemotherapy, and am here to tell you — have all symptoms checked out!”

# Genetic Counseling

## BRCA1/BRCA2 Testing, Screening

Of all the risk factors for ovarian cancer, none surpasses that of a woman who has a first-degree relative with ovarian cancer from a familial ovarian cancer family. Approximately 5% to 10% of all ovarian cancer is believed to be caused by an abnormal (mutated) gene inherited from the mother or father. If a mutation is identified in the BRCA1 or BRCA2 gene in an individual with cancer, their siblings and/or children are at a 50% risk to have inherited the same mutation. Identification of a mutation in the BRCA1 or BRCA2 gene confers an increased risk for ovarian cancer over the general population risk for ovarian cancer of 1.8% (or 1 in 55 women). Based on research involving familial cancer families, it was found that having one or more close relative(s) i.e., (mother, sister, daughter) with ovarian cancer increases your risk of ovarian cancer. Based upon family history alone, the risk increases from 1.8% to 5% (if you have one affected relative) or 7% (if you have two affected relatives).

BRCA1 and BRCA2 gene testing is recommended for individuals with a family history of ovarian or breast cancer and those of Ashkenazi Jewish ancestry. However, all such testing must be preceded by genetic counseling to ensure that the person is being tested for the appropriate genes (as there are other genes known to play a role in hereditary ovarian cancer), and has a thorough understanding of the risks, benefits and limitations of genetic testing (it is not always black and white).

Mutations in BRCA1 and BRCA2 are currently associated with a probability of developing ovarian cancer between 27% and 44% by age 70. For female carriers of BRCA1 or BRCA2 mutations, the lifetime risk for developing breast cancer is between 56% and 87% by age 70. These women are also at increased risk for a second breast cancer. Men with a BRCA1 or BRCA2 mutation are at increased risk for male breast cancer and prostate cancer. Two major refinements in genetic testing have made analysis of cancer risk more meaningful. First, when a person with ovarian or breast cancer carries an abnormal BRCA1 or BRCA2 gene, her healthy first-degree relatives (mother/father/sister/brother/daughter/son) can be tested to see if they have the same specific mutated form of the gene(s). If so, the evidence would be convincing that the healthy relative is at elevated risk for cancer, as noted above. Importantly, even if ovarian or breast cancer in a particular

family is due to a mutation in either BRCA1 or BRCA2 with a 50% risk for inheritance (from a person with a mutation), these genes confer susceptibility, not a certainty for the development of cancer. Having knowledge of this susceptibility is helpful in deciding appropriate screening, prevention and medical management approaches for a particular individual at increased risk. Second, even without a family history of ovarian or breast cancer, 2%, or 1 in 50 individuals, of Ashkenazi Jewish ancestry, from Central and Eastern Europe, are known to carry one of three specific BRCA1 or BRCA2 mutations. For BRCA1, the mutations are 185delAG and 5283insC and for BRCA2 – 617delT. Ashkenazi Jewish individuals can be tested for these three mutations.

In 1994, the first gene, BRCA1, and in 1995, the second gene, BRCA2, responsible for some inherited ovarian and breast cancers, were discovered. This led to the immediate belief that a simple, inexpensive genetic test (examination of DNA from white blood cells for abnormal (mutated) forms of the genes) could be available to any woman and be able to predict risk for cancer. However, a simple blood test for detecting mutations of these genes was not forthcoming because, to date, there are over 600 different mutations of the BRCA1 gene and 500 mutations of the BRCA2 gene, so inherited BRCA1 or BRCA2 mutations are most often different in different families. Thus, if genetic testing is appropriate, it is recommended to first test a family member with ovarian or early onset breast cancer to determine if a mutation is present; this forms the basis for interpreting test results in relatives at risk.

For women with a family history of ovarian cancer, cancer screening and surveillance should include pelvic and abdominal examination, CA125 blood levels and transvaginal ultrasound every six months, beginning between 25 and 35 years of age. Genetic consultation is recommended for any individual concerned about risk for ovarian cancer due to a family history. Cancer genetics professionals provide a risk assessment, information about causes of cancer, appropriate screening, surveillance and prevention measures, as well as potential genetic testing considerations. This can potentially allow you and your doctor to consider the best health care approaches while better understanding your cancer risk. It will also tell you more about who in your family may be at risk, and what actions they should take.

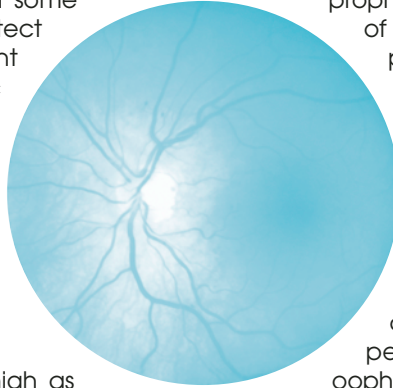
# Prophylactic Oophorectomy

In our 1979 paper, "Familial Ovarian Cancer," before the onset of the Registry, we wrote that "until some adequate screening tests which can detect pre-malignant or very early malignant ovarian tumors is discovered, prophylactic oophorectomy seems indicated in women in these ovarian cancer families. Because most cancers in these families occur after the early reproductive years, oophorectomy can probably safely be postponed until childbearing is completed."<sup>1</sup> To say the least, some considered this a radical concept in 1979.

Because ovarian cancer risk may be as high as 50% in women with a strong family history of ovarian cancer (two or more first- or first- and second-degree relatives with ovarian cancer), the Registry continues to advise these women to consider undergoing prophylactic oophorectomy (removal of normal ovaries and fallopian tubes) by age 35, if they have completed their families.<sup>2</sup>

However, with today's knowledge of genetics, it is advised that women at high risk of ovarian cancer consult with genetic counselors prior to surgery. Research has shown that most women over estimate their chances of having a mutation in the BRCA1 or BRCA2 genes and that they are not well informed about the mutations and the risks they pose.<sup>3</sup> This over estimation and lack of accurate knowledge regarding risk may affect women's risk management decisions and treatment. Determining actual risk for ovarian cancer and whether oophorectomy is indicated is extremely important. Women with family histories of ovarian cancer are at increased risk for developing ovarian cancer and some may be at increased risk for carrying mutations that are related to inherited cancer syndromes. In addition to syndromes associated with mutations in BRCA1 and BRCA2 genes (most commonly associated with breast and ovarian cancer), there may be increased risk of mutations in other genes associated with different hereditary cancer. It is critically important to identify the correct syndrome affecting a family so that the appropriate genetic testing and risk management strategies are employed. For this reason, the Registry recommends women to consult with a genetics counselor when contemplating a prophylactic oophorectomy to decrease their risk of developing cancer.

Prophylactic oophorectomy (without hysterectomy) by video laparoscopy is recommended due to low morbidity and minimal disruption to the lives of these women. During the procedure, the pelvis and abdomen should be examined carefully. Both ovaries should be completely submitted for pathologic evaluation to preclude missing a very small ovarian cancer.



Although women cannot develop ovarian cancer after prophylactic oophorectomy, a small percentage of women with a family history who have the procedure develop a papillary carcinoma of the peritoneum that is identical in histological appearance to ovarian cancer. Because of this concern, the Registry surveyed the first 931 families – 2,221 cases – entered between 1981 and 1992. Of 324 women who had undergone prophylactic oophorectomy, six (1.8%) developed primary papillary carcinoma of the peritoneum, one to 27 years after prophylactic oophorectomy.<sup>4</sup> Although peritoneal carcinoma after prophylactic oophorectomy is considered relatively uncommon, women considering this procedure should be made aware of this risk. These women should be evaluated after prophylactic oophorectomy by physical examination and CA125 annually or every six months.

Another advantage of prophylactic oophorectomy in women known to have a BRCA1 or BRCA2 mutation is not only the prevention of ovarian cancer but also the fact that there is a near 50% decreased breast cancer risk.<sup>5</sup>

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3. Bluman LG, Rimer BK, Berry DA, Borstelmann N, Iglehart JD, Regan K, Schildkraut J, Winer EP. Attitudes, Knowledge, and Risk Perceptions of Women with Breast and/or Ovarian Cancer Considering Testing for BRCA1 and BRCA2. *Journal of Clinical Oncology* 17:1040-1046, 1999.
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# HEALTH INSURANCE/EMPLOYABILITY

## FOR WOMEN WITH A FAMILY HISTORY OF OVARIAN CANCER

The issue of genetic information and health insurance has and will receive a great deal of attention as federal health care policy evolves. The 1996 Health Insurance Portability and Accountability Act (HIPAA) is the only federal law that directly addresses the issue of genetic discrimination. HIPAA was passed by Congress in part to prohibit group health plan insurers from using genetic information to deny coverage or limit eligibility. HIPAA applies to all covered entities, of which insurance plans are one. HIPAA prohibits positive genetic test results from being considered as a pre-existing condition and the use of genetic information to deny health insurance coverage, charge higher individual rates, or drop coverage based on genetic status. Some advocacy groups have recommended that individuals pay for genetic testing themselves, ask their physicians not to put the results in their medical record but instead keep them in a high security file, and purchase any insurance policies before genetic testing.

Currently, although several bills have been introduced, no federal laws comprehensively protect against employers using genetic information in the workplace. However, as of 2002, 47 states have enacted some form of legislation prohibiting genetic discrimination, to protect against discrimination on the basis of genetic testing. Twenty-seven states have enacted laws prohibiting insurance companies from requiring genetic testing or disclosing genetic information to a third party without prior written consent. Eighteen states have enacted laws providing that no employer may require genetic testing or may use the results of genetic testing or genetic information to discriminate in employment. The U.S. Equal Employment Opportunities Commission ruled in 1997 that under the Americans with Disabilities Act (ADA), a genetic susceptibility to disease is a protected disability. Therefore, individuals deemed a high insurability risk by an employer cannot be denied employment because of their genetic history. However, this interpretation has not been tested in the courts. Although there is no evidence of a relationship between unexpressed genetic factors and the ability to perform one's job, most experts recommend prohibiting access to genetic testing information in the workplace. Even when individuals are covered by health insurance, there may be situations when coverage is denied for a specific treatment or procedure related to genetic dis-

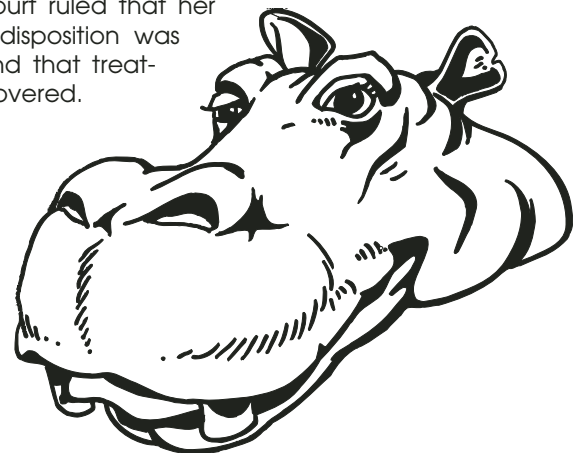
eases or disease susceptibility. There are no clear-cut precedents for setting legal policy. The Federal courts have never decided a genetic testing case. A lawsuit brought against Burlington Northern Sante Fe was settled for \$4.4 million in August 2000. The railroad had sought genetic testing to determine whether workers complaining of carpal tunnel syndrome were predisposed.

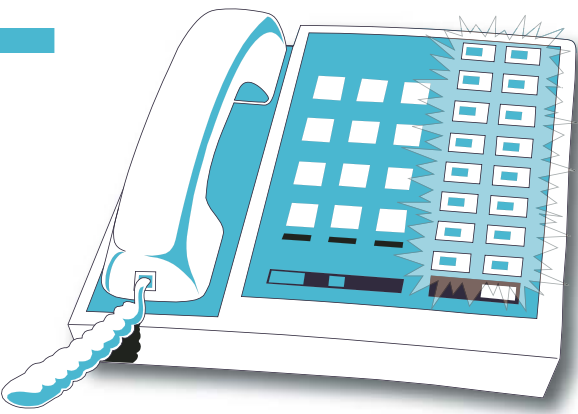
A second suit is pending in Florida by a woman fired by her employer after a genetic test showed she had a rare disease called alpha-1 antitrypsin deficiency, which sometimes results in emphysema or liver disease.

Federal employees have been protected from genetic discrimination for two years under an executive order signed by former President Clinton. The U.S. Congress has debated a number of bills since, but none have passed. The EEOC anticipates a genetic anti-discrimination bill to be reintroduced in the next session.

Also, it is encouraging that in May 1994 a decision by the Nebraska Supreme Court required an insurance company (Blue Cross/Blue Shield of Nebraska) to provide coverage for prophylactic oophorectomy and hysterectomy. The case involved a woman from a family with a history of ovarian cancer, who was considered to have a 50% risk of inheriting the gene responsible for the disease.

The woman's mother and maternal aunt had died of ovarian cancer in their late 40s and her younger sister had developed breast cancer. The insurance company denied coverage for prophylactic oophorectomy claiming that the woman's condition (hereditary cancer predisposition) was not an illness. The Nebraska Supreme Court ruled that her genetic predisposition was an illness and that treatment was covered.





# HELPLINE COMES TO A CLOSE



*Dianne Schuh, Co-Founder  
and Coordinator of the  
Gilda Radner Familial Ovarian  
Cancer Registry Helpline*

Over the years, volunteers, who have a personal and/or family history of ovarian cancer, have assisted callers in making decisions about their health care. Volunteers at the Helpline provided callers with information, along with emotional and personal support. After 10 years of dedicated service, the Helpline will close in June of 2006. The Registry staff does not believe this is an unhappy occasion as the Gilda Radner Familial Ovarian Cancer Registry Helpline comes to a close. In the past year the calls coming in for assistance have dwindled. There is a vast amount of information available to women today on the internet as women take command of their health care. With the closing of the Helpline, the staff of the Registry want to express our depth of gratitude to those dedicated volunteers who supported this line and helped so many women make informed decisions about their future health care.

The 800-Ovarian Hotline remains in effect, manned by Cancer Information Specialists at Roswell Park Cancer Institute to answer questions about ovarian cancer.

## For Information

For more information on or to add families to the Gilda Radner Familial Ovarian Cancer Registry, please contact:

Dr. M. Steven Piver or Cathy Fahey  
Gilda Radner Familial Ovarian Cancer Registry  
Roswell Park Cancer Institute  
Elm and Carlton Streets  
Buffalo NY 14263  
[www.ovariancancer.com](http://www.ovariancancer.com)  
or call 1-800-OVARIAN (1-800-682-7426)

**The Gilda Radner Familial Ovarian Cancer Registry**  
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**Dianne Schuh**  
Volunteer Coordinator

**Alice S. Whittemore, PhD**  
**Bruce A.J. Ponder, PhD**  
Consultants

**Gene Wilder**  
Honorary Chairman

## Thank YOU!

The Registry staff and volunteers join me in thanking each of you for making the past 25 years possible. It is because you care enough about the future generations of women that we are able to conduct our research and continue to maintain this Registry. We are very appreciative of your efforts and would like to recognize your continued interest and dedication to this project.



Cathy Fahey

# 25 Year Anniversary Polo Shirt



This great Polo shirt can be yours for a \$20.00 donation. Please call the GRFOCR at 1-800-685-6825 ext 4503 to order or visit our website at [www.ovariancancer.com](http://www.ovariancancer.com)  
Sizes: S, M, L, XL, XXL

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*Melissa McKinstry, Registry member, runs the NYC Marathon and raises over \$1,000 in donations for the Registry's ovarian cancer research in memory of her mother, Christine Osuch.*



*Members of the Board for Pansy's 2nd Annual Ovarian Cancer Golf Outing in Virginia Beach raised \$4,000 for ovarian cancer research this year and in two years has given the Registry \$8,000.*

## GRFOCR

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