



Help-Line for High Risk Women

A telephone Support Service for Women at High-Risk of Developing Ovarian Cancer.

Being at high risk for ovarian cancer (women with a family history of two or more first- or first- and second-degree relatives with ovarian cancer) can be frightening and confusing. There are serious decisions to make about your future health care.

The Gilda Radner Familial Ovarian Cancer Registry HELP-LINE for high risk women was established in 1994 to help women make educated decisions with confidence. Volunteers at the HELP-LINE want women to have the facts, along with the emotional and personal support they may need during this difficult time.

By calling 1-800-OVARIAN (1-800-682-7426) and asking for a HELP-LINE callback, you will be placed in contact with concerned volunteers who have made the decisions you are now facing.

HORMONE REPLACEMENT THERAPY: Risk of Breast or Ovarian Cancer

This section on Hormone Replacement Therapy (HRT) in the last issue of the Gilda Radner Familial Ovarian Cancer Registry Newsletter started out stating that “of the many issues that affect women from families with familial ovarian cancer, three recent reports in 2001 on hormone replacement therapy (HRT) may be the most confusing... not only to the women involved, but also confusing to the physicians trying to advise their patients.” With four scientific publications commencing July 17, 2002 and ending October 1, 2003, the confusion concerning HRT for women with a family history of ovarian cancer, already genetically at increased risk for ovarian and breast cancer would appear to have abruptly halted. The first unfavorable news came in an article in *JAMA* on July 17, 2002, which by now almost everyone is familiar with, titled “Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women.”¹ Postmenopausal women, ages 50-79, who had not had a hysterectomy were randomly assigned to estrogen plus progestin (Prempro) daily or a placebo pill. The women receiving estrogen plus progestin had a 26% increase in invasive breast cancer, a 29% increase in heart attack rate, 41% increase in the rate of stroke and a double rate of leg and pulmonary blood clots.

In that same issue of *JAMA*, in a study titled “Menopausal Hormone Replacement Therapy and Risk of Ovarian Cancer,”² researchers retrospectively reviewed a 1979-1998 study of former participants in the Breast Cancer Detection Project, a nationwide breast cancer screening program. Although this retrospective analysis does not rise to the scientific level of the Women’s Health Initiative prospective randomized placebo control trial, this study has some

disquieting results. The good news was that women who took estrogen plus progestin had no increase in the development of ovarian cancer as compared to women who had never taken HRT. However, those women who had taken estrogen alone compared to women who had never taken HRT had a 60% increase in the development of ovarian cancer, and those women who had taken estrogen alone after combined estrogen plus progestin had a 40% increase in the development of ovarian cancer, implicating estrogen alone as a possible causative factor in ovarian cancer.

In August 2003 in the journal *Lancet*, researchers reported on a study titled “Breast Cancer and Hormone Replacement Therapy in the Million Women Study.”³ In this retrospective study of one million British women who had taken HRT at the time the study was initiated in 1996 there was a 66% increased risk in the development of breast cancer and a 22% greater risk of dying from breast cancer by 2002. The risk for women taking estrogen plus progestin was approximately double the risk of women not taking HRT. For women taking estrogen alone, the increased risk was 30%.

Finally, in the October 2003 issue of *JAMA*, the Women’s Health Initiative reported on the development of gynecologic cancers in a paper titled “Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures.”⁴ In this randomized placebo control trial of 16,608 postmenopausal women who had not had a hysterectomy and received either estrogen plus progestin or placebo women randomized to estrogen plus progestin had a 58% increased risk in the development of ovarian cancer compared to those receiving placebo. The authors concluded that “this randomized trial

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 law 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 (EEOC) 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 relation 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 diseases 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 antitrypsan 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.



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. Since familial ovarian cancer is thought to be inherited as an autosomal dominant pattern, if a mutation is identified in the BRCA1 or BRCA2 gene in an individual 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 of 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 (mother, sister, daughter) with ovarian cancer increases your risk of ovarian cancer from 1.8% to 5% (if you have one affected relative or 7% (if you have two affected relatives).

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] applicable to any

woman would identify who would actually inherit the mutated gene and predict risk for cancer. However, a simple blood test for 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 and inherited BRCA1 or BRCA2 mutations are most often different in different families. Moreover, the estimated risk for developing ovarian or breast cancer if one carries the abnormal gene changes as more research information becomes available.

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. 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/sister/daughter) 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 ovarian or breast cancer. 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, 2% or 1 in 50 individuals of Ashkenazi Jewish ancestry, whose families originated from Central and Eastern Europe, are known to carry specific BRCA1 or BRCA2 mutations. For BRCA1, the mutations are 185delAG and 523insC and for BRCA2-617delT. Ashkenazi Jewish individuals, even those without a family history of ovarian or breast cancer, could be tested for these mutations.

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).

For women with a family history of ovarian cancer, 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.

Dear Dr. Piver,

I am writing to share with you a story about intuition, knowing and knowledge. I am writing so that other women will read my story and pause to think about the power of a woman knowing her body.

While sharing heating pads, old wives tales and remedies, my sister, my mother and my aunts all discussed having suffered from endometriosis. We were stunned and shocked when my sister was diagnosed with ovarian cancer at age 35. Once in remission my sister encouraged us to register with the Gilda Radner Familial Ovarian Cancer Registry. Learning that genetic factors are a significant factor in 10% of ovarian cancer, through the registry, I became educated about ovarian cancer – the most lethal type of gynecological cancer. I vowed to be an aware, well educated woman and follow through with recommended screenings by my physician. I wanted to know all there was to know.

Living in New York City, I set out to find a good doctor. With my family history of endometriosis, my neighbor recommended me to a gynecologist who specialized in endometriosis. I made regular visits, became familiar with risk factors for gynecological “problems” and went about the business of being a single young woman starting a career and living in the most exciting city in the world.

One morning severe abdominal cramping woke me and prevented me from standing up, let alone getting out of bed. My physician recommended a laparoscopy “for the endometriosis” and scheduled out-patient surgery. I recall him visiting me in the pre-operative holding area and showing me the x-rays. “Everything is fine,” he told me, “however, endometriosis is like cobwebs being spun in an unused uterus, the best advice I could give you is to get pregnant. That would prevent a reoccurrence of endometriosis.” “Odd advice, but he knows best,” I thought to myself.

Within the year I was back in his office with complaints of pain, abdominal cramping and just not feeling “right.” Once again, as he wrote out a prescription for pain medication, he again suggested I have a baby. Six months later I scheduled an appointment, not for confirmation of a pregnancy test, but because I did not “feel right.” I knew something was wrong. Following my examination, I met with my doctor in his office. I stared at yachting photos on the wall as he suggested that the my knowledge of familial risk was causing me to be “hyper vigilant.” He advised me that some pain, bloating, and weight gain was normal. I walked out of the office feeling like a foolish little girl – not a confident, well educated young woman. I was confused as to what to believe. On one hand, I knew how I felt. On the other hand, the doctor was an expert who treated women for gynecological problems everyday. So, I decided to trust the expert and ignore what my body was telling me.

One year later I went to the emergency room for severe cramping. I underwent emergency surgery, was diagnosed with ovarian cancer and began aggressive chemotherapy.

Today, as an ovarian cancer survivor and psychotherapist, I empower others to believe in their own intuition. I knew something was not “right.” I knew my body was telling me something but I did not listen to my own internal voice. It wasn’t because I was afraid of following my intuition, or I doubted myself. Rather, I let someone else silence me. Everyday we hear the persuasiveness of “expert” influences telling us what we should or shouldn’t believe, and what will happen if we ignore these beliefs. Fear becomes the constant companion of beliefs, and causes us to quiet the intuitive knowing deep down inside. My hope is that my experience will empower women to trust and believe in their own intuition. That it will encourage the women ‘to speak up and speak out’ when it comes to their bodies. And, more importantly, that it will encourage physicians to listen to their patient’s internal “knowing” which says something is not “right.” Intuition is powerful and heeding it can be empowering.

During my journey through cancer, I learned to trust in my intuition. I now trust the ebb and flow of the universe. I trust that life is bigger than what I can see and I trust that there is a divine order beyond my control. And I learned that when I trust myself, no matter what happens, I will be all right.

Sincerely,

Victoria

Prophylactic Oophorectomy

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) by age 35, if they have completed their families.^{1,2}

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. 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(s). 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 consult with a genetics counselor when contemplating a prophylactic oophorectomy to decrease their risk of developing cancer.³

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. 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.⁴

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.⁵



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HORMONE REPLACEMENT THERAPY

(continued from page 1)

suggests that continuous combined estrogen plus progestin may increase the risk of ovarian cancer.” The word “may” was advisedly used because the 58% increase was not statistically significant and there were only 32 cases of ovarian cancer.

Still not completed is the Women’s Health Initiative randomized trial on estrogen alone versus placebo in women who had previously had a hysterectomy. The results of this trial are expected in 2005.

In summary, these studies clearly implicate combined estrogen plus progesterone with a significant increased risk for breast cancer, strongly imply that estrogen alone increases the risk for ovarian cancer and that combined estrogen plus progesterone may also increase the risk of ovarian cancer. What these studies don’t resolve is the safety of short term combined estrogen plus progestin or estrogen alone for the tens of millions of postmenopausal women suffering from debilitating hot flashes, night sweats and even vaginal dryness. Hopefully, this issue will be resolved in the not too distant future.

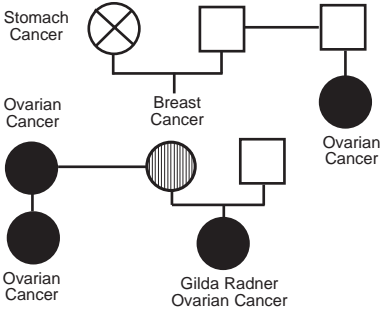
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A Message from **Gene Wilder**

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 change 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.

From: *Gilda’s Disease: Sharing Personal Experiences and a Medical Perspective on Ovarian Cancer*, M. Steven Piver, MD with Gene Wilder, Prometheus Books, Amherst, NY 1996.



Gilda’s family pedigree illustrates her family history of ovarian cancer (●), and breast cancer (◐). In past generations, ovarian cancer might have been known as “stomach” cancer.

Registry Research

The Gilda Radner Familial Ovarian Cancer Registry continues research into causes of familial ovarian cancer in collaboration with investigators at Roswell Park Cancer Institute, Stanford School of Medicine and Cambridge University. Goals are to: 1) identify new genes associated with familial ovarian cancer and 2) characterize lifestyle choices (oral contraceptive use, hormone replacement therapy, number of pregnancies) that reduce ovarian cancer risk in women who may be more susceptible to the disease. We hope to acquire information that will lead to better methods for detecting ovarian cancer and for preventing the disease in future generations; the ultimate goal of the Registry.

For Information

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

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Gilda Radner Familial

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Or call 1-800-OVARIAN (1-800-682-7426)

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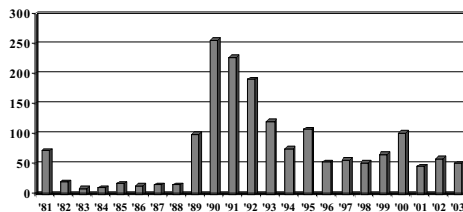
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The Gilda Radner Familial Ovarian Cancer Registry



Comedian Gilda Radner died May 20, 1989, after a long, courageous battle against ovarian cancer. Regrettably neither she nor her husband, Gene Wilder, ever knew that Gilda’s family history of ovarian and breast cancer put her at a very high risk of developing ovarian cancer. To date, the Registry, renamed in her honor in 1989, has enrolled 1,750 families with two or more close relatives with ovarian cancer. Most have been enrolled since Gilda’s struggle with ovarian cancer and her family history became known to the public.