# Ovarian Cancer: Peer Reviewed Analysis

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## Ovarian Cancer

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Ovarian cancer is an uncommon but very serious form of cancer. The overall lifetime risk of developing ovarian cancer for a woman in the U.S. is about 1.5 percent. Nearly thirty-thousand women are diagnosed with this disease each year, and about two-thirds of these women already have advanced disease at the time of diagnosis (Tortolero-Luna and Mitchell 1995). The fact that the disease is often detected at a late stage makes ovarian cancer the fifth leading cause of cancer deaths for women in the United States. Over the past few decades, there has been a very slight increasing incidence of ovarian cancer of about 0.1% per year. Although survival rates have increased slightly due to advances in chemotherapeutic regimens, five year survival is still only at 40 percent (Whittemore 1994; Ozols et al.1997).

The vast majority of ovarian cancers are of the epithelial cell type. This disease is extremely rare before age 40, but the incidence rate then increases until women reach their early 70's and then the incidence decreases again slightly (Whittemore 1994). Ovarian cancer is much more common in women living in North America or Europe than in the rest of the world. However, although rates of the disease have remained fairly steady in high-risk countries, a more significant increasing trend has been reported from previously low-risk countries (Tortolero-Luna and Mitchell 1995).

### Risk Factors for Ovarian Cancer

As is the case with breast cancer, hormonal, environmental and genetic factors play roles in the risk for developing the disease. For example, nulliparity (having no children) has been shown to increase risk of the disease, whereas multiple pregnancies and increasing duration of lactation decrease risk. A woman who has had three children has half the likelihood of developing ovarian cancer compared to one who has had no children (Whittemore et al.1992). These findings imply that breast cancer and ovarian cancer may share some of the same hormonal causes.

In contrast to breast cancer risk, no clear associations have been found between risk of ovarian cancer and age at menarche, age at first pregnancy, or age at menopause (Whittemore et al.1992). Women who take oral contraceptives for prolonged periods of time appear to have a

lower risk of ovarian cancer. This effect is most pronounced after more than three years of use. Tubal ligation and hysterectomy also have been reported to be protective (Daly and Obrams 1998). Several studies, however, have found that use of estrogen-only forms of hormone replacement therapy, or estrogen-progestin sequential therapy may increase the risk of ovarian cancer (Lacey et al. 2002; Riman et al. 2002)

**Genetics and Ovarian Cancer**

Increased risk of ovarian cancer has been associated with family history. Women whose mother or sister had the disease have a lifetime risk of disease around 9 percent. A small fraction of these cases have been traced to mutations of the so-called breast cancer genes, BRCA1 and BRCA2. Possessing a mutation of one of these genes confers a lifetime risk of breast or ovarian cancer in excess of 85 percent. However, family history appears to account for only 4-5 percent of cases of ovarian cancer, meaning that most cases are related to environmental or lifestyle factors (La Vecchia 2001).

In the U.S., white women have a risk of ovarian cancer about 50 percent greater than black women. Although the known risk factors appear to operate similarly in black women and white women, less than 20 percent of the observed difference in ovarian cancer rates between these two groups can be explained by differences in these known risk factors (John et al. 1993).

Women with one or more Jewish grandparents have more than double the odds of having ovarian cancer compared with women reporting no Jewish grandparents (Harlap et al. 2001). This may be due to the higher prevalence of the BRCA genes in women of Jewish background. Greater risk of ovarian cancer has also consistently been reported among women living at more northern latitudes across countries and within single countries such as France, Italy, and Japan. It is unclear whether these geographic differences reflect different patterns of reproduction, genetic differences, or differences in environmental factors. One study that attempted to tease apart the observed geographic differences by asking about the origin of grandparents found no effect of ancestral latitude. This suggests that the observation of increased risk in more northern latitudes is related more to environmental factors than to genetic origins.10 On the other hand, this same small hospital-based study did find some evidence of risk differences among non-Jewish women with different European origins, with lower risks among women whose grandparents originated in more westerly countries, corresponding with certain European genetic groups.

Several studies have investigated specific genetic differences and their relationship to ovarian cancer. For example, the cytochrome P450 (CYP) 1A1 gene has been investigated because of its critical role in detoxifying many environmental carcinogens such as those found in smoke and soot -- the polycyclic aromatic hydrocarbons (PAHs). In addition, the CYP1A1 gene has a role in the metabolism of estrogen, helping to guide whether estrogen is de-activated or instead, whether estrogen is converted into a byproduct that has been linked to genetic mutations. One study in Turkish women found that a specific sub-type of the CYP1A1 gene (Val allele) is associated with an approximately six-fold increased risk of ovarian cancer as well as of benign ovarian

tumors (Aktas et al. 2002). A study of nearly three hundred women in Hawaii, focusing on the CYP1B1 gene, also found an association with the Val allele. In this study, possession of two copies of the Val allele conferred nearly four-fold increased odds of ovarian cancer in all ethnic groups studied (Caucasian, Asian, and Native Hawaiian) (Goodman et al. 2001). In this study, use of oral contraceptives weakened the observed association, whereas cigarette smoking strengthened the association between the genetic subtype and cancer.

The discovery that certain genetic sub-types of the cytochrome P450 enzyme pathway may be associated with increased risk of ovarian cancer is an important one. This finding may help to explain some of the genetic propensity and racial variability seen in this disease, because the subtypes of this gene vary in different racial and ethnic groups, and are heritable in families. In addition, this discovery may lead to important revelations about ways in which genetic susceptibility may interact with environmental factors to create ovarian cancer.

**Environmental Factors and Ovarian Cancer**

**Sunlight, Vitamin D, and Exercise:** The observation that ovarian cancer may be more common in northern countries generated a hypothesis that vitamin D may be protective against ovarian cancer. Vitamin D is naturally produced in the skin on exposure to sunlight, and has been reported to have anti-cancer properties. An ecologic study found that fatal ovarian cancer in the U.S. is inversely related to the average annual intensity of local sunlight (Lefkowitz and Garland 1994). A nutritional study in Mexico reported that higher intake of retinol and vitamin D was associated with lower rates of ovarian cancer (Salazer-Martinez et al. 2002). A National Cancer Institute study investigated associations between exposure to sunlight and death from a variety of cancers (Freedman et al. 2002). Ovarian cancer risk was significantly lower in sunnier geographic regions within the U.S., but women whose jobs involved more exposure to sunlight did not show any decrease in risk.

Physical activity could theoretically reduce the risk of ovarian cancer because it decreases estrogen levels, reduces body fat, and reduces the frequency of ovulation. In addition, at least one study reported that women who are overweight in their late teenage years have approximately a 40% increased risk of later developing ovarian cancer (Lubin et al. 2003). However, in reality, there is no consensus as to whether physical activity increases or decreases the risk of ovarian cancer (Cottreau et al. 2000). Contradictory results have been seen in studies evaluating physical activity during leisure time and at work. A fairly large Italian study found lower rates of ovarian cancer among women reporting more physical activity at work, particularly among those women who reported active jobs during their younger years (Tavani et al. 2001). This study failed to find much evidence of an association with leisure activity level. In the U.S., a questionnaire study asking about leisure physical activity at various ages also found no links between activity level and ovarian cancer, except possibly at the most vigorous level of physical activity (Bertone et al. 2002). The large Nurses' Health Study followed over 92,000 cohort members for sixteen years, during which 377 women developed ovarian cancer.

Surprisingly, women who reported vigorous levels of physical activity had an increased risk of ovarian cancer in this study. The increased risk associated with physical activity was approximately 30-80% (Bertone et al. 2001).

**Occupational Exposures: Solvents, Aromatic Amines, and Organic Dusts:** Some of the research into ovarian cancer has focused on occupation. For example, some studies have reported associations between ovarian cancer and work in the dry cleaning industry, health care industry, and agricultural industry, whereas other studies have shown no increased risk of the disease among women working in these industries (Shen et al. 1998). Work in the graphics and printing industries has been repeatedly associated with an increased risk of ovarian cancer, with estimates ranging from a 60% increased risk to more than a doubling of risk of the disease (Shen et al. 1998). Because the graphics and printing industry often involves use of solvents, these chemicals have been implicated. Occupations in the telephone industry are associated with a 30% increased risk of the disease in several studies, raising questions about electromagnetic field (EMF) exposures (Sala et al. 1998).

More recently, a large study conducted in Sweden took advantage of the excellent Swedish census, as well as the cancer and death registries (Shields et al. 2002). All women who were employed during the 1960 or 1970 census were followed until December 1989. During that period, a total of nearly 1.7 million women were included in the study and nearly 9,600 cases of ovarian cancer occurred in these women. Occupational codes were used to classify likely exposures to factors as diverse as sunlight, heavy lifting, pesticides, diesel exhaust, solvents, and radiation. Because it is difficult for experts to accurately extrapolate occupational exposures simply from job and industry data, there was probably extensive misclassification in this study. Misclassification of this type tends to result in underestimates of any true associations between an exposure and a disease. On the other hand, because the study looked at large numbers of occupations and industries, there is a distinct possibility that apparent associations could occur by simple statistical chance. This large study supported some previous findings such as the increased risks in the graphics and printing industry and the telephone industry. Some of the most dramatic associations were among women who worked in the paper and packaging industry, as well as in the lumber and carpentry industry. These women had more than a doubling of their risk of ovarian cancer. Workers in the textile and shoe industries were also at increased risk. The authors noted that carcinogenic aromatic amines are commonly used as dyes in the shoe industry, graphics industry, and textile industry. Organic dusts are commonly found in the textile, leather, wood, and paper industry. This study did not find any association between ovarian cancer and exposure to solvents, pesticides, electromagnetic fields, sunlight, and physical activity.

**Talc and Ovarian Cancer:** The potential association between use of talc powders in the genital area and development of ovarian cancer is extremely controversial. Talcum powder may be applied directly to the genital area after bathing, or may be sprinkled on sanitary napkins. In addition, talc may be used on condoms or on diaphragms. One experimental study found that

carbon particles deposited in the vagina can travel up into the fallopian tubes within 30 minutes, implying that talc applied to the genital area may also do so (Egli and Newton 1961). A pathology study done in the early 1970's found embedded talc particles in 75% of ovarian tumors sampled (Henderson et al. 1971). Talc has been suspected for many years because it is chemically related to asbestos, and because talcum powders in the past were contaminated with asbestos fibers. Women occupationally exposed to asbestos have been reported to have an increased risk of ovarian cancer (Keal 1960). In addition, one of the most common types of ovarian cancer, invasive serous cancers, very closely resemble mesotheliomas. Mesothelioma is a type of cancer that is specifically associated with exposure to asbestos. On the other side of the debate, several studies in which talc was injected directly into the ovaries of rats failed to identify significant increases in ovarian cancer (Wehner 2002).

Several retrospective studies comparing women with ovarian cancer and similar women without the disease, have reported apparent associations between talc usage and ovarian cancer. Some of these studies have reported only marginal associations, whereas others have reported risks up to nearly 2.5-fold (Chang and Risch 1997). Twelve fairly large case-control studies reported associations between talc exposure and ovarian cancer, whereas three small studies did not find any association. One study of more than a thousand women found that 45% of women with ovarian cancer reported using talc in their genital area, compared to 36% of women without the disease, leading to an overall increased relative risk of about 60%. Women who did not themselves use the powder, but whose husbands regularly used talc on their genitals also had a 50% increased risk of ovarian cancer. The only women in this study who failed to show such an association were those who had previously had a tubal ligation, implying that closing off the pathway from the external genitals to the ovaries may be protective (Cramer et al. 1999). In addition, use of talc prior to pregnancy was associated with a much higher risk than talc usage after pregnancy, implying that changes may occur in the ovary during pregnancy that may decrease susceptibility. The authors of this study predicted that approximately 10% of ovarian cancer cases in the general population may be attributable to talc usage.

The increasingly persuasive body of research on talc and ovarian cancer was called into question in February of 2000, when a prospective study was published looking at this issue as part of the very large Nurses' Health Study (Gertig et al. 2000). Among the over 78,000 women in the cohort for analysis, 307 women were diagnosed with ovarian cancer by June of 1996. Previously, in 1982, all the women had answered questions about talc use in the genital area. The question was phrased to ascertain whether they had 'ever' used talc, making it difficult to ascertain when the usage occurred or whether it was ongoing. In this study, there was no overall association between use of talc and ovarian cancer, even when the researchers attempted to take into consideration numerous factors that could affect the association. However, there was approximately a 40% greater report of ever using talc among those women who later developed serous invasive ovarian cancers. The serous cell type accounts for more than half of all invasive

ovarian cancers, has been linked to asbestos, and was previously associated with talc in another study.

A combined analysis of sixteen studies on talc and ovarian cancer included a total of 11,933 women (Huncharek et al. 2003). The pooled results of this analysis showed an overall 33 percent increased risk of ovarian cancer with talc use, which was statistically significant. However, the authors of the analysis nonetheless questioned the validity of this result for two reasons: first, there was no clear dose-response relationship where women who reported more or longer use of talc were at higher risk, and second, the studies that used comparison patients who were hospitalized with other diseases did not find any difference in talc usage, and only the studies that used healthy women for comparison found an association. The authors believed that this could mean that flaws in study design might explain the apparent association.

**Herbicides and Atrazine:** A Italian study of women with ovarian cancer compared to women with other types of cancer found that those with ovarian cancer were 2.2-times more likely to be classified as "probably exposed to herbicides" (based on questionnaire information). Women with ovarian cancer were 4.4-times more likely to be classified as "definitely exposed", due to reported personal use of an herbicide (Donna et al. 1984) . As in all questionnaire-based studies, the actual exposure was not measured and the possibility of errors in recollection exists.

Members of the same research group undertook a second case-control study in 1989; this one was in the general community, rather than hospital-based. They compared 69 women with ovarian cancer to women from the same municipal regions. On the basis of questionnaire data, they found that women with ovarian cancer were 1.9 times more likely to have been "possibly exposed" to triazine herbicides and were 2.7-fold more likely to be classified as "definitely exposed" according to their questionnaire responses (Donna et al. 1989). Triazine herbicides include chemicals such as atrazine, simazine, and cyanazine. Atrazine is the highest volume herbicide used in the United States, where it is chiefly used on corn crops in the Midwestern states and on sugarcane in Florida. Atrazine is the most commonly detected pesticide in streams, rivers, and lakes, and is present in the drinking water in some areas. Although atrazine does not cause ovarian cancers in laboratory animals, it is known to interfere with ovarian cycling by disrupting the pituitary gland hormones that regulate ovarian function. Pigs treated with relatively low doses of atrazine in one study developed multiple ovarian follicular cysts and cystic degeneration of secondary follicles, a picture consistent with abnormal stimulation of ovarian tissue (Gojermac et al. 1996).

**Summary**

Ovarian cancer is almost certainly caused by a combination of genetic, hormonal, and environmental factors. It appears that hormonal cycling and ovulation may, over time, promote the development of ovarian cancer. Potential environmental links such as solvents, dyes, organic dusts (paper dust, wood dust) and triazine herbicides are based on very limited scientific data and remain uncertain. Vitamin D may be somewhat protective against the development of ovarian

cancer. The data on the possible link between talc exposure and ovarian cancer are conflicting and do not permit a definite conclusion. However, it appears that there may be an increased risk associated with the use of talc in the genital area.

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