

# **Risk Factors for Ovarian Cancer: An Overview**

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## ***Abstract***

Ovarian cancer is the fifth most frequent cancer among women and is the leading cause of gynaecological cancer deaths in North America. Although the etiology of ovarian cancer is not clear, certain factors have been implicated in the etiology of ovarian cancer such as: ovulation, gonadotropic and steroid hormones, germ cell depletion, oncogenes and tumor suppressor genes, growth factors, cytokines, and environmental agents. Other factors that may play a role in the etiology of ovarian cancer include: personal or family history of breast, ovarian, endometrial, prostate or colon cancer, hereditary nonpolyposis colorectal cancer or syndrome, increasing age, infertility, no history of birth control pill usage, use of high dose estrogens for extended periods, cigarette smoking, obesity, and exposure to certain environmental agents such as talc, pesticides, and herbicides. Oral contraceptive use has been shown to be protective against ovarian cancer, with ovarian cancer risk decreasing with duration of use.

Epidemiologic studies, animal experiments, and receptor binding studies suggest that malignant ovarian tumors may be endocrine-related and hormone-dependent. These studies have led to the hypothesis that exogenous estrogenic compounds may play a role in the etiology of this cancer. The lack of adequate animal studies and well-designed epidemiological studies limits our ability to describe the association between ovarian cancer and environmental estrogens. Further epidemiological and toxicological research is needed to strengthen the database on which an assessment of risk factors for ovarian cancer can be made.

## ***Introduction***

Ovarian cancer is the fifth most common type of cancer among women, and ranks first among the different types of gynaecological cancer mortality in Canada (Canadian Cancer Statistics, 2004). Ovarian cancer mostly affects elderly and middle-aged women, with the highest incidence rates reported in North America and Northern Europe, and the lowest in Japan and in developing countries (Greenlee et al., 2000). Over the past 40 years, the rate of ovarian cancer mortality has increased among women 65 years of age and older. The incidence of ovarian cancer increases with age, from 1.5/100,000 annually among women 20-30 years of age to 49/100,000 in women 60-69 year of age (Mant and Vessey, 1995). In Canada, 2,500 new cases are reported annually, and 1,550 women die from this disease each year. The lack of screening tests for early diagnosis of ovarian cancer is an important determinant of the mortality rate from this disease. Because of the absence or subtlety of early symptoms, more than 70 % of patients are diagnosed with advanced stages of ovarian cancer (Goff et al., 2000).

The increase in the incidence of ovarian cancer near the age of menopause can be related to the diminution of oocytes or germ cells, the reduction in circulating estrogen levels, or a significant increase in the pituitary gland's production of the gonadotropic hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]). Ovulation, growth factors, cytokines, and environmental agents may play a role in the initiation and progression of ovarian cancer (Vanderhyden et al., 2003). Ovarian cancer begins with transformation of cells that comprise the ovaries, including surface epithelial cells, germ cells, and the sex cord or stromal cells. The surface epithelial cells are the primary locus of ovarian cancer, with almost 90% of all ovarian cancers derived from the surface epithelium (Weiss et al., 1977).

The etiology of ovarian cancer is not completely understood. Known risk factors for ovarian cancer are related to hormonal and reproductive factors, including nulliparity, late age at menopause, and family history of ovarian and breast cancer. Oral contraceptive use has been shown to be protective against ovarian cancer, with risk decreasing with duration of use. Epidemiologic studies, animal experiments, and

receptor binding studies suggest that malignant ovarian tumors may be endocrine-related and hormone-dependent (Lacey et al., 2002, Dowsett 2000, Davis et al., 1993, Gillesby and Zacharewski 1998). These studies have led to the hypothesis that exogenous estrogenic compounds may play a role in the etiology of this cancer.

The present review of published epidemiological studies was conducted to identify the risk factors related to ovarian cancer. This overview was prepared in response to concerns about the possible association between ovarian cancer and environmental toxicants that may act by hormonally mediated mechanisms. In order to better understand the role of such environmental agents, it is important to examine all potential risk factors for ovarian cancer. This overview will also serve to identify gaps in knowledge and research needs for ovarian cancer that will address primary prevention and early detection of this disease. Elucidation of the etiology of ovarian cancer may be accomplished both through animal experiments and population based epidemiological studies of women at risk of ovarian cancer.

### ***Risk Factors***

The etiology of ovarian cancer is not very clear. However, some hypotheses about the etiology of epithelial ovarian tumors have been advanced (Modugno et al., 2003). The incessant ovulation hypothesis suggests that proliferation and repair of the surface epithelial cells following ovulation may increase the chance of an abnormal repair process, leading to a malignant cell and subsequent development of ovarian cancer (Fathalla, 1971). Under this hypothesis, any factor that inhibits or prevents ovulation would reduce the risk of ovarian cancer. The pituitary gonadotropin hormone hypothesis suggests that high levels of gonadotropins can directly, or indirectly through the increased production of estrogen, stimulate ovarian surface epithelial cells in inclusion cysts and leads to malignant transformation (Konishi et al., 1999). Any factor that increases the level of these hormones can increase the risk of ovarian cancer (Modugno et al., 2003).

Other risk factors for ovarian cancer include: personal or family history of breast, ovarian, endometrial, prostate or colon cancer; hereditary nonpolyposis colorectal cancer or syndrome; increasing age; infertility; nulliparity; no history of birth control pill usage, use of high dose estrogens for long periods; lifestyle, and exposure to certain environmental contaminants. Each of these factors will be considered in more detail below.

## **Family History**

Epidemiologic studies have indicated that after controlling for age, the strongest risk factor for ovarian cancer is a family history of ovarian cancer. The incidence of ovarian cancer attributable to genetic factors is estimated to be in the range of 5 to 10% (Risch et al., 2001). Women with one first-degree relative with ovarian cancer have a 5 % lifetime risk and women with two or more first-degree relatives have a 7 % risk. The risk is greater for the sisters and daughters than for the mother (Cook, 2002). Women with a family history of three or more cases of ovarian cancer are more likely to develop ovarian cancer at a younger age (Goldberg et al., 1997). The hereditary component of ovarian cancer appears to be due to mutations in BRCA genes, with two-thirds of those cases linked to BRCA1 gene mutations and one-third associated with BRCA2 (Frank et al., 1998).

Roughly 1 in 800 women in the general population carry BRCA1/2 mutations. In Ashkenazi Jewish women, the ratio is about 1 in 50 (Roa et al., 1996). Hereditary factors for ovarian cancer require further investigation, as women with BRCA1/2 mutations are 10 times more likely to develop ovarian cancer than women without these mutations (Boyd et al., 2000).

## **Reproductive Factors**

There is epidemiologic evidence that late menopause may be associated with an increased risk of ovarian cancer (Franceschi et al., 1991). Other studies have found no relationship

between age at menarche and the risk of ovarian cancer (Purdie et al., 1995). The frequency of ovulation and the development of epithelial ovarian cancer appear to be related (Purdie et al., 2003). Incessant ovulation is an important determinant of ovarian cancer risk, with factors that suppress ovulation, such as pregnancy, use of oral contraceptive pills (OCP), and lactation, reducing the risk of ovarian cancer (Purdie et al., 2003). Evidence continues to accumulate that nulliparity is associated with an increased risk of ovarian cancer (Bristow et al., 1996). Infertile women who received fertility drugs for extended periods of time are at higher risk of developing ovarian cancer (Rossing et al., 1994). Overall, multiparous women have a 30 to 70% lower risk as compared with nulliparous women (Mosgaard et al., 1997).

## **Hormone-Dependency**

Some epidemiologic studies indicated that ovarian cancer is endocrine-related and hormone-dependent (Dowsett, 2000, Lacey et al., 2002, Davis et al., 1993, Gillesby and Zacharewski 1998). Exposure to estrogens during different periods in a woman's life has been associated with the risk of ovarian cancer. The most common sources of exposure to hormones for women are the use of hormone replacement therapies and oral contraceptives.

## **Hormone Replacement Therapy (HRT)**

The ovaries naturally produce estrogen before menopause, but produce gradually lower levels of estrogen, progesterone, and testosterone as menopause progresses. HRT usually involves treatment with either estrogen alone or in combination with progestin to compensate for decreased hormonal levels at menopause. Although the association between HRT and ovarian cancer remains unclear, several recent case-control studies have found an increased risk of epithelial ovarian cancer in relation to the use of HRT (Riman et al., 2002, Lacey et al., 2002,). Lacey and colleagues observed a significant association between estrogen replacement therapy (ERT) and ovarian cancer among women who have used estrogen only for 10 or more years. However, there was no

significant increase in ovarian cancer for women who used estrogen-progestin (EPRT) for a short period of time.

A meta-analysis of 9 case-control studies reported a statistically significant association for ever use of ERT (OR=1.15, 95% CI: 1.05-1.27) as well as for more than 10 years of ERT use (OR=1.27, 95% CI: 1.00-1.61) (Garg et al., 1998). In contrast, another meta-analysis of 15 studies concluded that ERT does not increase the risk of ovarian cancer (Coughlin et al., 2000). A recent prospective study of 944 fatal ovarian cancers among 211,581 post-menopausal women who used ERT for 10 or more years indicated a two-fold increase in the risk of ovarian cancer mortality (Rodriguez et al., 2001). However, additional data on long-term ERT and EPRT use, including dose, dosing regimen, and duration of use, may be necessary to confirm these findings.

### **Oral Contraceptive Pills (OCP)**

Oral contraceptives are man-made versions of natural female hormones, which are similar to the hormones produced by the ovaries and contain combinations of estrogen and progesterone or a progestogen alone. The association between female reproductive organ cancer and use of OCP has been studied for decades, with OCP consistently shown to reduce the risk of ovarian cancer. Ever use of OCP has been shown to decrease ovarian cancer risk by 40 to 50% compared with never use (Purdie et al., 1995; Rosenberg et al., 1994). The reduction in risk appears greatest following more than 10 years of use (Key, 1995). Moreover, there is some evidence that low doses of oral contraceptives confer substantial protection against the development of ovarian cancer (Royar et al., 2001). In addition, women with a family history of ovarian cancer appear to be at reduced risk of ovarian cancer with increasing duration of OCP use (Narod et al., 1998). Another study suggested that 4 to 8 years of OCP use can halve the risk of cancer in women with a family history of ovarian cancer by age 70 years, as compared to non-users (Walker et al., 2002).

## **Lifestyle**

Although the incidence rate of ovarian cancer in Japan is significantly lower than in western countries, a remarkable change in lifestyle after World War II has increased the mortality rate by almost 4-fold (Li et al., 2003). This observation suggests that lifestyle may play a role in the etiology of ovarian cancer. There is some evidence that smoking, physical activity, diet, and alcohol consumption can affect ovarian cancer risk, as described below.

### **Obesity and Physical Activity**

Obesity alters the endogenous hormones due to excess adiposity (which favour conversion of androgen to estrogens in adipose tissue). This could increase the chance of infertility, which in turn, has been related to elevated ovarian cancer risk (Harris et al., 1992). Analyses of the Nurses' Health Study have indicated that recent body mass index (BMI) and adult weight change have no relationship with ovarian cancer. On the other hand, higher BMI in young adults (18 years of age) was associated with a two-fold increased risk of premenopausal ovarian cancer (Fairfield et al., 2002). A review of 29 studies showed an association between BMI and ovarian cancer, with a mean of 1.2 based on cohort studies and 1.4 based on case-control studies (Purdie et al., 2001). A nested case-control study based on 3 prospective cohorts in USA, Sweden, and Italy suggested a negative association between ovarian cancer and BMI, and a positive association with height in younger women (Lukanova et al., 2002). In some case-control studies height, weight, and BMI were unrelated to ovarian cancer risk; however, after stratification by menopausal status, these factors were positively associated with the risk of ovarian cancer among pre-menopausal but not post-menopausal women (Kuper et al., 2002).

There is some evidence to suggest that physical activity has a protective effect against ovarian cancer (Tavani et al., 2001; Cottreau et al., 2000). In a recent study, ovarian cancer risk was decreased (OR= 0.54, 95% CI: 0.34 -0.87) with increased frequency and duration of activity among pre-menopausal women (Zhang et al., 2003).

## **Diet**

Potential dietary risk factors for ovarian cancer that have received attention to date include: galactose, dietary fat, eggs, and fruit and vegetable consumption. Animal-derived food such as red meat, milk, and eggs may increase serum gonadotropins (FSH and LH), which may increase the risk of ovarian cancer by directly stimulating cell proliferation and inhibiting apoptosis in the ovarian surface epithelium (Konishi et al., 1999). Most studies have not identified a role for dietary fat and galactose intake in the development of ovarian cancer. Nonetheless, some studies have suggested that saturated fat consumption may result in an increased risk of epithelial ovarian cancer (Huncharek, 2001). A case-control study in Italy has shown that starch was directly associated with the risk of ovarian cancer and that unsaturated fatty acids were inversely associated with ovarian cancer risk (Bidoli et al., 2002). Bosetti et al (2002) noted a protective effect of olive oil and other vegetable oils against ovarian cancer has been seen in some case-control studies. Another study suggested that galactose intake might play a role in the development of borderline ovarian cancer among women who carry the rare galactose 1-phosphate-uridylyltransferase (GALT) N314D polymorphism (Cozen et al., 2002). The hypothesis that high consumption of either lactose or galactose enhances the risk of ovarian cancer seems to be strongly related to the fat content of many dairy foods (Webb et al., 1998). It has been suggested that raw (OR= 0.47), or cooked vegetables (OR= 0.65), fish (OR= 0.51), and pulses may decrease ovarian cancer risk, whereas, red meat (OR= 1.53) increases the risk of ovarian cancer (Bosetti et al., 2001).

## **Cigarette Smoking**

The available scientific evidence suggests that tobacco smoking impairs ovarian function, affects steroid hormone concentrations, and leads to reproductive problems (Zenzes, 2000). Tobacco smoke contains more than 60 recognized carcinogens (Hecht, 2002). Nicotine and its metabolites have been identified in ovarian granulosa-lutein cells. Reactive metabolites of benzo[a]pyrene contained in tobacco smoke form DNA adducts in granulosa-lutein cells and oocytes, thereby enhancing the risk of DNA damage (Zenses

et al., 1997). This genotoxic mechanism represents a plausible biological mechanism by which tobacco smoke may increase ovarian cancer risk.

The association between cigarette smoking and risk of ovarian cancer remains unclear, since different studies have produced positive, null, and negative results. Several case-control studies support a positive association between cigarette smoking and ovarian cancer. In most of these studies, the available evidence suggests a positive association between smoking and certain mucinous types of tumors (Marchbanks et al., 2000, Modugno et al., 2002). Long-term cigarette smoking was associated with an increased risk of epithelial ovarian tumors, with women who had smoked for years being at the highest risk (RR = 2.5, 95% CI: 1.3-4.5), as compared with women who had never smoked (Terry et al., 2003). Another population-based case-control study suggested that smoking is a risk factor for ovarian cancer, particularly mucinous and borderline mucinous lesions, among current smokers (OR = 3.2; 95% CI: 1.8-5.7) and former smokers (OR = 2.3; 95% CI: 1.3-3.9) (Green et al., 2001). There is evidence that indicates that smoking may play a role in the development of some types (mucinous) of ovarian cancer and not all types (Zhang et al., 2004).

In contrast, another case-control study of active and passive tobacco smoking did not provide evidence of a positive association with invasive ovarian cancer, but did demonstrate significant positive association with borderline serous ovarian tumors (Goodman and Tung, 2003). These apparently contradictory results may have resulted from the small sample sizes involved in these studies, differences in the ethnic composition of the study subjects, lack of information on possible confounding factors, and failure to examine histological types of ovarian cancer. Clearly, there is a requirement for studies with larger numbers of cases of each histological type to clarify the association between cigarette smoking and ovarian cancer risk.

## **Environmental Factors**

Since the female genital tract allows the movement of fine particulate matter from the outer vagina through the uterus and fallopian tubes to the surface of the ovary, it is possible that exogenous carcinogens may play a role in the induction of cancer of the ovary (Holschneider, 2000). Ovarian cancer may be affected by exposure to occupational and environmental agents, although existing information is insufficient to reliably describe the etiologic roles of such agents (Davis et al., 1993, Gillebsy and Zazherewski 1998).

## **Occupational Exposure**

In general, the results of occupational studies seem to be inconsistent and insufficient to draw conclusions about associations with ovarian cancer. The existing studies are ecologic or proportional mortality studies, and potential confounders have not been taken into account. The lack of data on lifestyle factors may influence the association between occupational exposures and ovarian cancer. Some occupations, such as dry cleaning, telegraph and telephone use, paper packaging, and graphics and printing are associated with elevated ovarian cancer rates (Shields et al., 2002). In a study of two printing plants, there was a significantly elevated incidence of ovarian cancer among bookbinders (Bulbulyan et al 1999). The available evidence suggests that exposure to organic dusts, paper dust, aromatic amines, aliphatic and aromatic hydrocarbons, solvents, man-made vitreous fibers, high levels of asbestos, and diesel and gasoline in the workplace may increase the risk of ovarian cancer (Vasama-Neuvonen et al., 1999, Bulbulyan et al., 1999, Langseth, 1999, Germani et al., 1999, Shield et al., 2002).

## **Environmental Contaminants**

Several investigators have hypothesized that exposure to environmental chemicals such as pesticides and herbicides can be linked to ovarian cancer. A case-control study of women with previous exposure to triazine herbicides showed a 2-3 fold increase in the risk of epithelial ovarian cancer, in comparison with unexposed women (Donna et al.,

1989). An association between atrazine and ovarian tumours has been observed in two Italian studies (Donna et al., 1984, 1989), suggesting that atrazine may be carcinogenic to humans. Aside from phenoxy acid herbicides, atrazine is the most commonly used herbicide worldwide (Short & Colborn, 1999), with application in the cultivation of corn, fruits, vegetables and grapes for producing wine. Atrazine has been classified as a possible human carcinogen by the International Agency for Research on Cancer (IARC, 1999). A study by Wetzel et al. also demonstrated that feeding Sprague-Dawley rats subjected to high doses of atrazine lengthened their estrous cycle, increased the number of days in estrous, and, given in conjunction with estrogen, induced an earlier onset of mammary tumors. Atrazine is a genotoxic compound, which induces DNA damage in some cells, and increases mammary and ovarian tumor incidence in rats following oral exposure (Wetzel et al., 1994).

Clinical and epidemiological studies also have suggested an association between cosmetic talc use and the risk of epithelial ovarian cancer (Cook et al., 1998). Talc particles are able to move through the reproductive system and attach to the lining of the ovary, remaining there for a sufficiently long period of time to cause ovarian cancer. Talc particles have been found in ovarian tumors, and women with ovarian cancer have reported the more frequent use of talcum powder in their genital area than healthy women (Chang et al., 1997). Although numerous studies have shown a strong link between frequent use of talc in the female genital area and ovarian cancer, there is no credible evidence to support the role of talc in the etiology of ovarian cancer (Huncharek et al., 2003). The lack of clear dose-response relationship, selection bias, and uncontrolled confounding factors may affect on inconsistency of the results. However, further study with consideration of the duration, frequency, and method of exposure must be conducted to examine the role of talc exposure and the risk of ovarian cancer.

## ***Conclusion***

Ovarian cancer is the most common cause of death from gynecologic malignancies in the western world. Considerable effort has been expended to date to link variations in

incidence in ovarian cancer rates with environmental, endocrinological, and genetic factors. There is growing evidence to suggest that factors such as family history, hormone therapy, lifestyle, and environmental exposure to certain chemicals may increase the risk of ovarian cancer. If current knowledge of the epidemiology of ovarian cancer is to be used as a basis for disease prevention, more attention should be paid to women at risk because of their family history, and educational strategies should be implemented to promote awareness of the protective effect of oral contraceptives. Pesticides with endocrine disrupting activity remain in use, legally or illegally, in different countries, including organochlorine, organophosphorous, arsenic and mercury compounds, phenoxy acid herbicides, atrazine, and dithiocarbamates. Scientific research to date suggests a link between atrazine and risk of ovarian cancer. Overall, certain environmental and occupational exposures may be associated with ovarian cancer. This association may be modified by life-style or genetic susceptibility. Although the collective evidence of an association between ovarian cancer and environmental agents is limited, environmental exposures should be considered in future studies of ovarian cancer.

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