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The Epidemiology of Ovarian Cancer

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Abstract Ovarian cancer is the second most common cancer of the female reproductive system and the leading cause of death from gynecologic malignancies. In 1995, 26,600 women will be diagnosed with ovarian cancer in the U.S., and 14,500 women will die from the disease. Between 1986–1990, the overall age-adjusted incidence was 14.3/100,000 women; mortality was 7.8/100,000 women. Ovarian cancer, rare before age 40, increases steeply thereafter and peaks at ages 65–75. Incidence and mortality rates are higher among white women than among African-American women. Over the last three decades, ovarian cancer incidence has remained stable in high-risk countries, while an increasing trend has been reported in low-risk countries. Despite recent advancements in treatment, the overall five-year survival rates continues to be low (39%). Over 70% of ovarian tumors are diagnosed when regional or distant involvement has already occurred, causing survival rates to remain stable.

The etiology of ovarian cancer is poorly understood. Most studies have focused on the epidemiology of invasive epithelial ovarian tumors, while few have explored the epidemiology of epithelial tumors of low malignant potential and nonepithelial tumors. Factors associated with an increased risk for invasive epithelial ovarian cancer include age, race, nulliparity, family history of ovarian cancer, and history of endometrial or breast cancer. Factors associated with a reduced risk are history of one or more full-term pregnancies, use of oral contraceptives, history of breast feeding, tubal ligation, and hysterectomy. Other factors such as infertility, fertility drugs, hormone replacement therapy, age at menarche, age at menopause, dietary factors, lactose intolerance, talc use, coffee and alcohol consumption have been suggested, but their role is still inconclusive.

Key words: Epidemiology, family history, ovarian cancer, risk factors

Ovarian cancer is the seventh most common cancers in women worldwide, after breast, cervix, colon/rectum, stomach, corpus uteri, and lung cancers. The highest incidence rates are observed in developed countries and the lowest in developing countries [1,2]. In the U.S., ovarian cancer is the second most common gynecologic cancer and the leading cause of death from gynecologic malignancies. It is estimated that in 1995, 26,600 new cases of ovarian cancer will be diagnosed in the U.S., and that approximately 14,500 women will die as a result of the disease [3]. The lifetime risk among women with no history of familial ovarian cancer is estimated to be 1.4% (1 in 70 women). Approximately 90% of all malignant tumors in the ovary are epithelial. Other histologic types occur less frequently: sex cord-stromal tumors (6%), germ cell tumors (3%), and tumors of indeterminate histogenesis (~ 1%) [4].

INCIDENCE, MORTALITY, AND SURVIVAL

Incidence rates for ovarian cancer show a wide geographic variation. The highest incidence rates are observed in Scandinavian countries, Israel (American- or European-born), and North

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America, while the lowest rates are observed in developing countries and Japan [1]. Geographic variations in ovarian cancer incidence are partially explained by inter-country differences in the accuracy of the reporting systems, socioeconomic development, fertility rates, patterns of oral contraceptive use and, hysterectomy rates.

The incidence of ovarian cancer has remained stable over the last three decades in high-risk countries, while a trend to increasing incidence has been reported in low-risk countries [5–7]. In developed countries, women born between 1861 and 1901 showed an increasing trend in ovarian cancer incidence; whereas women born after this period have declining incidence rates. The upward trend in older women is partially attributed to reproductive patterns, improvement in access to medical care, intensity of diagnosis, and accuracy of death certification; the decrease in incidence in younger women is attributed to oral contraceptive use and increasing rates of oophorectomies and tubal ligation [5–9]. From 1973 to 1990, the incidence rate from ovarian cancer fluctuated between 12.9 and 15.1 per 100,000 in the U.S. [10]. The slight increase (6%) in incidence of ovarian cancer over time has been observed among pre- and post-menopausal white women and among post-menopausal African-American women, but not among younger African-American women [10].

In the U.S., incidence rates are higher among white and Hawaiian women, intermediate among African-American, Hispanic, and Asian women, and lowest among Native American women [1]. During the period from 1986–1990, the incidence rate among white was 50% higher than among African-Americans (15 per 100,000 women versus 10.2 per 100,000 women) [10]. This ethnic difference, constant over time, has been observed in premenopausal (< 50 years old) and postmenopausal (≥ 50 years old) women. Ovarian cancer is rare before age 40, increases steeply thereafter, and peaks between the ages of 65 to 75. A similar age pattern is observed in both white and African-American women.

In England and Wales, as in the U.S., mortality from ovarian cancer increased with each successive cohort born after 1861, peaked among women born in the early 1900s, and then declined with each successive generation [7,8]. The increasing trend in mortality from ovarian cancer has slowed down since the mid-1970s. This trend is mainly attributed to a decline in mortality among women under 55 years of age and coincided in time and magnitude with the use of oral contraceptives. During the last two decades, the overall age-adjusted mortality rate from ovarian cancer declined approximately 7% in the U.S. However, the decrease in mortality has been limited exclusively to premenopausal women (40% reduction). The overall age-adjusted mortality rate for the period 1986–1990 was 7.8/100,000, and it was slightly higher among whites (8.0/100,000) than among African-Americans (6.4/100,000) [10].

More than 75% of ovarian cancer cases are still diagnosed in advanced stages of the disease and the relative five-year survival rate continues to be poor [10]. When ovarian cancer is detected and treated at early stages, the relative five-year survival rate can be as high as 88%; when detected in distant stages, survival is only 18%. Although there is no ethnic difference in relative five-year survival rates (39% in whites and 38% in African-Americans), a significant difference is observed with age. Survival rates are two times higher among women < 50 years old than among women ≥ 50 years (64% and 32%, respectively). This age difference in survival rates is larger in African-Americans than in whites [10].

FACTORS ASSOCIATED WITH OVARIAN CANCER RISK

The etiology of ovarian cancer remains unknown, but several factors have been consistently associated with decreased or increased risk of the disease. Most epidemiologic research has centered on the study of invasive epithelial ovarian tumors, while few have explored epithelial tumors of low malignant potential and nonepithelial tumors [9,11,12]. Reproductive factors have been extensively studied, but interpreting the results had been complicated by the intercorrelation of reproductive characteristics [13–21]. In addition, results from epidemiologic studies, mainly case-control studies, have been limited by small sample sizes, low participation rates, and potential bias in the selection of control groups. Despite these limitations, age, race, nulliparity, history of endometrial or breast cancer, and family history of ovarian cancer have been consistently associated with increased invasive epithelial ovarian cancer risk; parity, oral contraceptive

use, history of breast feeding, tubal ligation, and hysterectomy have been associated with a reduction in risk. The role of several factors, including age at menarche, age at menopause, infertility, use of fertility drugs, estrogen replacement therapy, talc use, dietary factors, lactose intolerance, and history of mumps and other infectious diseases, remain inconclusive. This paper reviews the most consistent factors associated with epithelial ovarian cancer risk.

Factors Associated With Decreased Risk

Parity. Parity, the most important "natural" factor affecting the risk of ovarian cancer [22], has been associated with a lower ovarian cancer risk. These findings were ratified by the pooled analyses by Whittemore *et al.* [23] of 12 case-control studies in the United States and by Negri *et al.* [22] of three case-control studies in Europe, and more recently by two large case-control studies in Canada [24] and Sweden [25]. Whittemore *et al.* [23] observed a significant risk reduction with any term pregnancy in both population-based studies (odds ratio (OR) = 0.47, 95% confidence interval (CI) = 0.40–0.56) and hospital-based studies (OR = 0.76, 95% CI = 0.63–0.93). Similar strong protective effects were observed in the European pooled analysis (OR = 0.7, 95% CI = 0.6–0.8) [22]; in Canada (OR = 0.39, 95% CI = 0.28–0.55) [24]; and in Sweden (OR = 0.64, 95% CI = 0.59–0.70 (crude OR estimated from data provided in article) [25]. The risk of ovarian cancer decreases with increasing number of pregnancies. However, it is suggested that the effect of first pregnancy may outweigh the effect of further pregnancies. However, risk reductions between 14% and 22% have been estimated with each additional birth [23–25].

Oral contraceptives (OCs). OCs have been consistently shown to reduce the risk of ovarian cancer. The effect of OCs is one of the best established and most consistent findings in the epidemiology of epithelial ovarian tumors [26–29]. Only two studies have not observed a reduction in ovarian cancer risk among OC users [15,30]. Estimates of risk from numerous epidemiologic studies range from 0.25 to 0.8 [26–29]. Prentice and Thomas [28] estimated an overall risk reduction of approximately 40% with OC use. These results have been confirmed by three recent meta-analyses [23,26,31]. The protective effect of OCs is observed independently of the study design (case-control or cohort study) and the selection of study population (population-based or hospital-based).

Epithelial ovarian cancer risk decreases with increasing duration of OC use; a consistent and clear decrease in risk is observed after five or more years of OC use [32–37]. Hankinson *et al.* [26] estimated that ovarian cancer risk decreases by 11% with each year of OC use and by 46% after five years of use; however, little additional protection is observed after six or more years of OC use [23]. The protective effect afforded by OC use appears to persist for a long period (10 or more years) after discontinuation [26,29,31]. A 50–70% reduction in risk has been reported in several studies 10 or more years after OC use ended.

A larger risk reduction was observed among women who had breast fed for longer periods compared with those who breast fed for shorter periods or did not breast feed. The protective effect conferred by OC use appears to be independent of parity, age at diagnosis, age at first OC use, or usual body mass index [26,33,34, 36,37]. Similarly, dose and type of OC formulations do not appear to modify this protective effect; however, the long-term effects of newer formulations will need further study. An interaction between OC use and length of breast feeding was suggested by the pooled analysis by Whittemore *et al.* [23].

Breast Feeding. Women with a history of breast feeding are reported to have a lower risk for ovarian cancer than nulliparous women and parous women who have not breast fed [23,33, 35,38,39]. This protective effect appears to persist after controlling for age, parity, and use of OCs. Women who have breast fed have a 60% reduction in risk compared with nulliparous women, and parous women who have breast fed have a 40% lower risk of ovarian cancer compared to parous who have not breast fed [39]. Whittemore *et al.* [23] detected a similar protective effect in population-based studies (OR = 0.81, 95% CI = 0.68–0.95) and hospital-based studies (OR = 0.73, 95% CI = 0.51–1.0). The risk of ovarian cancer decreases with increasing duration of breast feeding. Whittemore *et al.* [23] estimated that the risk decreases 0.99 with every month of breast feeding. In addition, the reduction in risk conferred by lactation appeared to be was larger in

the first six months after delivery than the reduction observed with subsequent months of lactation.

Tubal Ligation and Hysterectomy. Tubal ligation and hysterectomy with ovarian preservation have been associated with a decreased risk for ovarian cancer. Tubal ligation has shown a decreased risk ranging from 0.15 (95% CI = 0.027–0.88) to 0.87 (95% CI = 0.62–1.2) [23,40]. Whittemore *et al.* [23] estimated a 40% reduction in hospital-based studies and a 13% reduction in population-based studies in invasive epithelial ovarian cancer risk associated with tubal ligation. There was no association with age at surgery or time since surgery, although data suggested a greater risk reduction among women who had a tubal ligation before age 40 than in those who had tubal ligation when older. Using data from the Cancer and Steroid Hormone Study, Irwing *et al.* [41] observed a 30% reduction in epithelial ovarian cancer risk among women who had tubal ligation (OR = 0.69, 95% CI = 0.38–0.81), and in a large hospital-based case-control study in England, Booth *et al.* [42] also found a significant reduction in risk among women with tubal ligation (OR = 0.2, 95% CI = 0.1–0.6). Similar risk reductions were recently reported by Hankinson *et al.* [43] among women in the Nurses' Health Study (relative risk (RR) = 0.63, 95% CI = 0.16–0.64) and by Rosenberg *et al.* [37] in a large hospital-based case-control study in Boston, New York, Philadelphia, and Baltimore (OR = 0.6, 95% CI = 0.4–0.9). In contrast, Risch *et al.* [24] in Canada and Shu *et al.* [30] in Shanghai observed a small, nonsignificant reduction in ovarian cancer risk in women who had undergone tubal ligation; whereas Chen *et al.* [44] in Bejing, China, did not find an association.

Hysterectomy with ovarian preservation has also shown an inverse association with ovarian cancer risk in several studies [41,45,46]. In the pooled analysis by Whittemore *et al.* [23], hysterectomy without oophorectomy was significantly associated with a decreased risk in hospital-based studies (OR = 0.66, 95% CI = 0.50–0.86), but with a nonsignificant decreased risk in population-based studies (OR = 0.88, 95% CI = 0.72–1.1). Results from more recent studies have shown reductions in risk that range from 30% [47] to 80% [42]. Hartge *et al.* [47] observed a nonsignificant reduction in risk (OR = 0.7, 95% CI = 0.4–1.2) among women with hysterectomy without oophorectomy. In contrast, studies in England, Canada, and the U.S. observed statistically significant reductions in risk [24,37,41–43]. Although possible explanations for this protective effect have been suggested, such as increasing anovulation and blocking access of carcinogens to the ovary, several sources of bias should be considered in interpretation of these findings [46]. Among the potential biases are selective removal of cancerous ovaries, underreporting of bilateral oophorectomies among women who undergo hysterectomy, overrepresentation of women with hysterectomies among control groups, and increased screening among women who undergo tubal ligation or hysterectomy.

Factors Associated With Increased Risk

Family History. An association between ovarian cancer and a positive family history of ovarian cancer and other malignancies has been reported by several clinical and epidemiologic studies. Familial ovarian cancer is described by the occurrence of the disease in women with one or more first- or second-degree relatives affected with ovarian cancer [48]. Lynch *et al.* [48] points out that identifying a patient with familial ovarian cancer requires a detailed family history in order to identify a hereditary etiology. It is estimated that approximately 5–10% of ovarian cancers may be due to hereditary factors [49]. Three hereditary syndromes in which familial aggregation of ovarian cancer occur have been described: site-specific ovarian cancer syndrome, breast-ovarian cancer syndrome, and hereditary nonpolyposis colorectal cancer syndrome (Lynch Syndrome II). Susceptibility to hereditary ovarian cancer appears to be transmitted as an autosomal dominant genetic trait with incomplete penetrance and variable expression. Compared to the general population or to control relatives, the relatives of patients with hereditary ovarian cancer have an excess of multiple primary cancers, an early age at onset of the disease, and display a vertical transmission [48]. Furthermore, the risk of ovarian cancer appears to be greater for relatives of patients diagnosed before age 55 than among those diagnosed later (7.4 versus 3.7) [50]. However, these findings need to be interpreted with caution because relatives of patients (especially first-degree relatives) are more likely to see

a physician at an early age and to undergo more intensive screening than women without a family history of cancer.

Results from several case-control studies support this association of a positive family history of ovarian cancer. An increased risk for invasive ovarian cancer has been reported in women with a family history of ovarian and breast cancer and, less consistently, with history of endometrial cancer [6,9,15,16,19,51,52]. Schilkraut and Thompson [52] estimated an OR of 3.6 (95% CI = 1.8–7.1) among women with first-degree relatives with ovarian cancer and an OR of 2.9 (95% CI = 1.6–5.3) among women with second-degree relatives with ovarian cancer. The magnitude of the association was similar for all major histologic subtypes (serous, mucinous, and endometrioid). The association with ovarian cancer in first-degree relatives was only observed for malignant tumors (OR = 5.3, 95% CI = 2.5–10.8), but not for borderline tumors (OR = 0.0, 95% CI = 0.0–3.4) [52]. Using data from selected case-control studies, Kerlikowske *et al.* [53] estimated that the lifetime risk of ovarian cancer among women 35 years old associated with a family history of ovarian cancer was 5% for those with one first- or second-degree relative with ovarian cancer, 7% for those with two or three first- or second-degree relatives, and 50% among those with hereditary ovarian cancer.

Despite current evidence, the occurrence of familial ovarian cancer accounts for only a small proportion of ovarian cancer cases. In the study by Parazzini *et al.* [54], only 2.5% (18/734) of ovarian cancer patients reported having had a first-degree relative with ovarian cancer; in the CASH study [52], 7% of those aged 20–54 years had any family member with a history of ovarian cancer, 3.2% had a first-degree relative with ovarian cancer, and only 0.6% reported having more than one family member with a history of the disease. Similar percentages were observed by Koch *et al.* [51]; 4.6% (9/197) of the cases had a family history of ovarian cancer, and only 0.5% (1/9) reported having more than one relative with the disease. These data suggest that although family history increases the risk for invasive ovarian cancer, it is unlikely that genetic factors are exclusively responsible for the disease, underlining the importance of environmental and hormonal factors in ovarian carcinogenesis.

Infertility and Fertility Drugs. Although results from studies linking infertility and use of fertility drugs are far less consistent, the strength of the associations suggested by recent publications [23,55] warrant their inclusion in this review. Women reporting difficulty in conceiving have been found to have a higher risk for ovarian cancer, but this relationship remains inconclusive because of inaccuracies in the definition of "exposure." Many studies have not been able to differentiate between female and male infertility and between types of female infertility such as tubal or endocrine infertility. In addition, many women do not seek medical care for infertility or receive inadequate medical evaluation [6,9]. Whittemore *et al.* [23] found a non-statistically significant increased risk (OR = 1.4, 95% CI = 0.86–2.3) for ovarian cancer among ever-married nulliparous women who had a clinical diagnosis of infertility. The risk was higher among women diagnosed with infertility after 1970 (OR = 1.5, 95% CI = 0.67–3.3) than among women diagnosed earlier. Rossing *et al.* [55] also observed an increase in ovarian cancer among a cohort of infertile women (standardized incidence ratio (SIR) = 2.5, 95% CI = 1.3–4.5). Both studies suggested a higher risk for women with infertility of ovulatory etiology (OR = 2.1, 95% CI = 0.9–4.7 [23] and SIR = 3.7, 95% CI = 1.4–8.1 [55]) and a smaller, nonsignificant increased risk among women with infertility of tubal etiology (OR = 1.3, 95% CI = 0.63–2.8 [23] and SIR = 3.0, 95% CI = 0.4–10.8 [55]). Similar inconsistent results have been observed with the length of the period of unsuccessful pregnancy attempts among both nulliparous and parous women [23, 24], although several studies have shown an increased risk among nulliparous women with 10 or more years of unprotected intercourse [23,42].

Several published case reports of ovarian tumors among women with history of treatment for infertility suggest a role of fertility drugs in the etiology of the disease. Results from the pooled analysis by Whittemore *et al.* [23] and a cohort study of infertile women by Rossing *et al.* [55] appeared to support these clinical observations. Whittemore *et al.* [23] observed that infertile women treated with fertility drugs were at high risk of ovarian cancer compared to women without a history of infertility (OR = 2.8, 95% CI = 1.3–6.1); whereas, infertile women who did not use fertility drugs were not at increased risk.

The risk associated with the use of fertility drugs was higher among nulligravida women (OR = 27.0, 95% CI = 2.3–315.6) than among gravid women (OR = 1.4, 95% CI = 0.5–3.6). Rossing *et al.* [55] found statistically significant increased risk of ovarian tumors among women who used clomiphene (SIR = 3.1, 95% CI = 1.4–5.9), which was especially strong among those who used it for 12 or more cycles (SIR = 11.1, 95% CI = 1.5–82.3). Stronger effects were reported for borderline tumors [11,55]. Despite the magnitude of this association, several limitations should be considered in interpreting these results, particularly the small number of cases in these studies, potential recall, diagnosis and selection bias, and partial control of confounding factors. Additional, larger epidemiologic studies are need to assess this association.

CONCLUSIONS

The etiology of ovarian cancer is multifactorial. Several factors have been consistently observed to modify the risk of ovarian cancer; however, the roles of many other factors remain inconclusive. Although the proposed hypotheses to explain the pathogenesis of ovarian cancer (incessant ovulation and hypergonadotropic hypogonadism) appear to account for the majority of known risk factors, the explanation for some factors remains unclear. Furthermore, some reproductive and hormone factors appear to be in conflict with these hypotheses. More epidemiologic, clinical, and basic research is needed to clarify inconsistencies in the etiology of ovarian cancer. The identification of genetic markers will allow elucidation of the mechanisms of carcinogenesis. Further epidemiologic studies need to include histologic-specific analysis and address the effects of variation in reproductive patterns, current OC formulations, use of fertility drugs, and the interactions between genetic factors and environmental and reproductive characteristics.

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