der to diagnose epithelial tumors at a time when they are still confined to e pelvis and highly curable.

In patients with advanced cancer, treatment approaches are also changing. ew combination chemotherapy regimens are under evaluation in clinical trials which issues such as high-dose chemotherapy and dose intensity are being udied. It is our hope that this issue will provide to the reader an overview of e current approach to the management of this disease. In addition, we have ed to provide a framework to help understand the forthcoming new thera- eutic developments that are based on an ever-increasing understanding of the ology of this complex disease.

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THE EPIDEMIOLOGY OF OVARIAN CANCER

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Ovarian cancer is the leading cause of death from a gynecologic malignancy among women in the United States and accounts for approximately 12,500 deaths per year.[62] Although the etiology and pathophysiology of ovarian carcinogenesis are unknown, there is a growing body of epidemiologic literature that has identified several potential contributing factors. This article explores these findings, with a particular emphasis on the genetic and reproductive features characteristic of the disease.

GENERAL FEATURES

Ovarian cancer is a disease of older age, with incidence rates increasing with each decade of life and peaking in the mid to late 70s[77] (Fig. 1). The rate of rise in incidence appears to accelerate coincident with the time of natural menopause.[20, 64] Malignant ovarian tumors do occur in childhood and represent 1% to 3% of all pediatric malignancies, but approximately two thirds of these are of the germ cell type.[3, 17, 19]

Age-adjusted rates for ovarian cancer have remained relatively stable over the last two decades (Fig. 2), although mortality rates have climbed as a result of the aging of the population, and possibly owing to changing reproductive patterns.[16] Significant geographic and ethnic variations in rates have been observed. Rates are highest for white women in the industrialized countries of northern and western Europe and North America, and lowest in India and Asia.[53] The wide geographic variation observed is roughly correlated with average family size.[24] Within the United States, incidence rates for black, Hispanic, and American Indian women are approximately 40% lower than those for white women,[63] and among whites, rates are highest for Jewish

From the Cancer Control Science Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania

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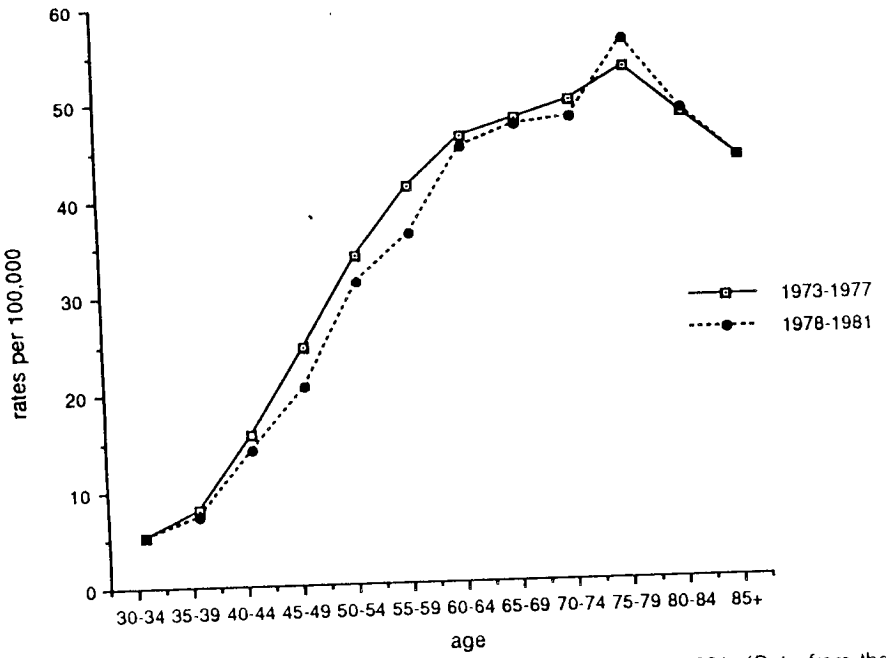

Figure 1. Ovarian cancer rates by age for 1973–1977 and 1978–1981. (*Data from* the SEER program: Cancer Incidence and Mortality in the United States, 1973–1981. US Department of Health and Human Services, 1984.)

women.[20, 31] These ethnic differences in rates may be partially explained by variations in reproductive factors.

ENVIRONMENTAL FEATURES

Both the observed international and ethnic variations, and the shift in risk to that of the host country among migrant populations,[29] suggest a role for an environmental component such as diet in the etiology of ovarian cancer. Numerous case control studies, however, have failed to show an association between either weight or dietary fat intake and the risk for ovarian cancer.[2, 31, 48, 69] A positive association between ovarian cancer risk and lactose consumption has, however, been found in a number of studies. Cramer[15] correlated ovarian cancer incidence with both per capita milk consumption and lactase persistence worldwide and found both to be significantly positively associated. A case-control study conducted in 10 Boston-area hospitals demonstrated both higher levels of lactose consumption and lower levels of galactose converting enzymes in cases than in controls.[16, 27] Although these data are very preliminary, there is theoretic support from the observation that women who suffer from galactosemia, an inborn error of metabolism resulting in elevated levels of serum galactose, often develop premature ovarian failure and hypergonadotropic hypogonadism.[15] A series of animal studies has also documented ovarian failure in rodents fed a high galactose diet.[65]

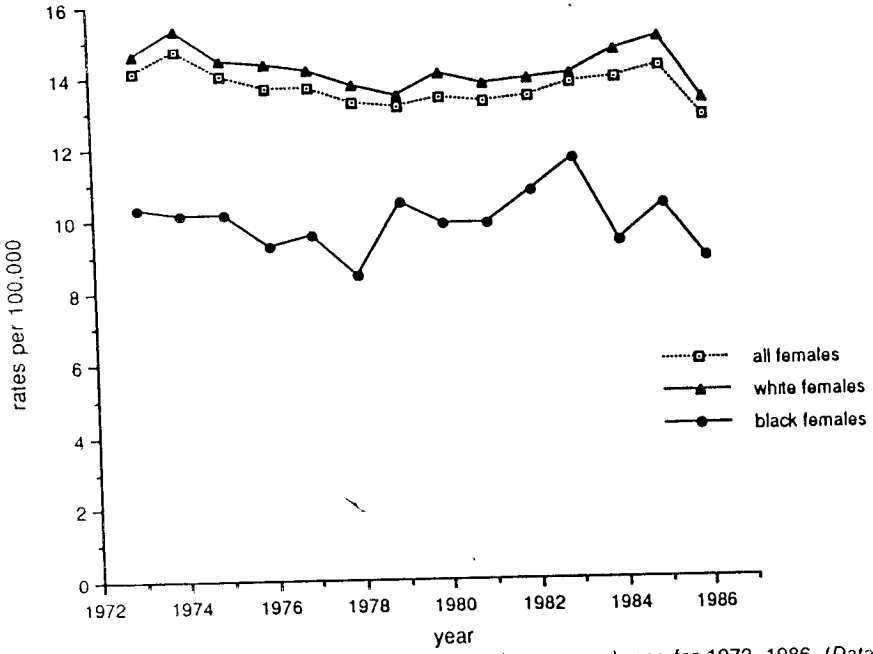

Figure 2. Age-adjusted ovarian cancer incidence by year and race for 1973–1986. (*Data from* the SEER program: Cancer Statistics Review, 1973–1986. US Department of Health and Human Services, 1989.)

Other environmental factors that appear to be unrelated to risk for ovarian cancer are occupation, alcohol, and smoking history.[34, 48] The noted increased incidence among women of higher socioeconomic status most likely reflects the combined effects of reproductive history and differential access to health care.[20]

Of all the environmental factors implicated as causative agents in ovarian cancer, none has generated as much interest as talc and asbestos particles. Talc is a specific hydrous magnesium silicate that is chemically related to asbestos. Asbestos fibers are often found as contaminants of talc consumer products.[1] Interest in these compounds as causative agents for ovarian cancer stems from the recognition of asbestos as a cause of pleural and peritoneal mesothelioma, a disease that shares a common embryologic origin with ovarian cancer.[1] Henderson et al[30] first reported finding talc particles in ovarian tissue obtained from nine women, three of whom had ovarian cancer. Cosmetic talc is thought to gain access to the ovaries by absorption through the vagina or cervix. In a case-control study in Boston, Cramer et al[10] reported a relative risk of 1.9 among individuals who used talc directly on the perineum or on sanitary pads. Whittemore et al[73] also showed a weak association between talc use and risk for ovarian cancer, but there was no dose-response relationship. Although these data are provocative, they offer only indirect evidence for an association between these products and ovarian cancer. With the removal of talc from most cosmetic preparations over the last decade, the issue may remain unresolved.

Likewise, with the introduction of widespread vaccination among childre

against mumps, the causative role of this virus may never be clarified. First thought of as a potential etiologic agent for ovarian cancer because of its known association with clinical orchitis in males, mumps also belongs to the paramyxovirus family, which is associated with a number of rare but fatal chronic diseases.[47] Two case-control studies have found a lower self-reported history of mumps infection among cases[13, 47]; however, when serum antibody levels were measured, they were similar for cases and controls, suggesting that ovarian cancer patients with mumps were more likely to have experienced subclinical disease, which may have led to subsequent chronic damage to the ovaries, depletion of oocytes, and alterations in gonadotropin levels.[47]

Finally, there is evidence from the survivors of the atomic bomb experience that high doses of radiation increase the risk for ovarian cancer, particularly among those women who were less than 20 years of age at the time of exposure, with a latent period of approximately 20 years.[68]

GENETIC FACTORS

Although the recognition of a hereditary component to ovarian cancer is very recent, heredity is emerging as one of the most important aspects of the disease. The number of known multicase ovarian cancer families has increased several-fold over the last 10 years. Extensive pedigree analysis by Lynch et al[39, 42] has led to the recognition of three patterns of familial ovarian cancer: (1) site-specific ovarian cancer only; (2) families in whom both breast and ovarian cancer predominate; and (3) the cancer family syndrome characterized by multiple cases of ovarian, breast, colon, and uterine cancer. Through careful analysis of these pedigrees, an autosomal dominant mode of inheritance with variable penetrance is postulated. A subset of approximately 5% to 10% of all ovarian cancers are thought to fit this genetic pattern.[25] The most common relationship reported among cases is sibship, followed by mother-daughter.[22, 54] Among these pedigrees, there is a significant reduction in risk for breast/ovarian cancer for relatives as their levels of coancestry decrease.[39] Other characteristics of familial ovarian cancer include an earlier age at onset and evidence of both paternal and maternal transmission[41, 43]; however, there does not appear to be a significant difference in stage at presentation, histologic type or grade, or bilaterally between familial and sporadic cases.[22, 25] The familial aggregation of ovarian cancer demonstrated by these pedigree analyses has been confirmed in numerous case-control studies. Data from the Alberta Cancer Registry have documented a statistically significant increase in affected family members among cases of ovarian cancer.[35] Tzonou et al[69] found a familial aggregation of ovarian cancer among women with breast, ovarian, and uterine cancer in Greece. In Japan, Mori et al[48] found a family history of breast, uterine, and ovarian cancer to be more common in cases than in controls. Using the multicenter data base assembled by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, Schildkraut and Thompson[60] demonstrated an odds ratio for ovarian cancer of 3.6 in first-degree relatives, and 2.9 in second-degree relatives, as compared with relatives of controls. The excess of affected relatives was seen in both maternal and paternal lines. Of interest is the fact that neither the SEER data nor a case-control study conducted by Harlow et al[26] in Washington state could demonstrate an increased risk of ovarian cancer for relatives of women with borderline tumors, suggesting a different carcinogenic pathway for this subtype of ovarian cancer.

The familial aggregation of breast and ovarian cancer is supported by data from the Cancer and Steroid Hormone (CASH) Study,[7] a population-based case-control study conducted by the Centers for Disease Control, in which Thompson and Schildkraut[67] were able to demonstrate an elevated risk of developing breast cancer among first-degree relatives of women with ovarian cancer.

Finally, lending further support to a proposed genetic mechanism for ovarian cancer is the finding of clustering of both breast and ovarian cancer in the patients themselves. Data from the Birmingham Cancer Registry in England found a significant excess of second primaries in premenopausal women with either breast or ovarian cancer. Prior and Waterhouse[57] and Greggi et al[25] report a fivefold increase in rates of breast cancer occurring as a second primary among familial ovarian cancer cases, as compared with sporadic ovarian cases.

Although the precise genetic defect(s) associated with familial ovarian cancer has not yet been identified, a number of genetic alterations and associations have been described. Several investigators have noted decreased levels of α-L-fucosidase among women with ovarian cancer and their first-degree relatives,[5, 40, 55] suggesting close linkage of the genetic loci that control α-L-fucosidase activity and ovarian carcinogenesis. Cytogenetic characterization of surgical specimens from ovarian tumors reveals extensive and complex structural chromosome abnormalities involving chromosomes 1, 3, 6,[21, 72] chromosome 14,[70] and chromosome 17.[51, 52] Marks et al[45] reported overexpression of the p53 gene, a gene recently linked to familial breast cancer,[44] in 50% of 107 tumor samples. This growing body of evidence points to a multistep model of ovarian carcinogenesis in which a complex series of genetic events result in the initiation, development, progression, and metastatic potential of the disease.

REPRODUCTIVE FACTORS

Because the ovary is the major source of reproductive hormones in women, it is only natural that a great deal of attention has been paid to the role of reproductive factors in trying to understand the etiology of the disease. The one overwhelming observation that has emerged from almost every study in the literature is the relationship between pregnancy experience and risk for ovarian cancer. Women who develop ovarian cancer are significantly more likely to be nulliparous and to have had fewer pregnancies.[23, 34, 48-50, 66] The relative risk associated with nulliparity ranged in several case-control studies from 1.5 to 3.2.[2, 6, 12, 18, 33, 46, 48, 76] Furthermore, there is a clear dose-response relationship associated with pregnancy history, with most studies reporting a steady decrease in risk with increased parity.[6, 12, 31, 33, 48, 49, 76] When controlled for number of pregnancies, however, age at first pregnancy does not appear to affect risk.[4, 6, 12, 38, 76] The role of oral contraceptive pills (OCPs), which mimic some of the physiologic changes induced by pregnancy, has also been carefully studied with regard to ovarian cancer. OCPs were first introduced in the United States in the 1960s. Most formulations include estrogen, progesterone, or a combination of the two, and they have been shown to suppress ovulation. Women with a history of OCP use have an overall reduction in risk of ovarian cancer of 40%.[56] The largest case-control study to document this effect was that conducted by the Centers for Disease Control, using the population-based cancer registry data of the eight SEER regions, and age-matched and area of residence-matched community controls. Ever-users of OCPs had a relative risk for ovarian cancer of 0.6. Risk reduction was apparent with as little as 3 months of use, increased in magnitude with duration of use, and persisted for as long

as 10 years after discontinuation of use.[9] The observed reduction in risk applied to all histologic subtypes, including borderline tumors, and was not dependent on age at use, menopausal status, or measures of fertility or parity, although nulliparous women experienced a greater decrease in risk than did parous women.[8] A summary of similar findings from a number of case-control studies is shown in Table 1. Note that the majority of these studies failed to show a relationship between replacement hormone therapy for menopausal symptoms and risk for ovarian cancer.[2, 6, 31, 46] One exception is a case-control study in Washington state in which replacement hormone use was associated with a relative risk of 3.1 for the histologic subset of endometrioid tumors.[71] A similar trend was noted in a study in Boston by Cramer et al,[12] and in a case-control study in Washington, DC.[28] Endometrioid tumors of the ovary are similar in appearance to tumors of the endometrium and may share common risk factors No clear-cut relationship between age at menarche or age at menopause and risk for ovarian cancer has emerged from these studies.

Another series of studies investigated the role of sterilization procedures on subsequent risk of ovarian cancer. Irwin et al[32] examined the data from the Centers for Disease Control study to compare histories of tubal sterilization and hysterectomy with or without unilateral oophorectomy between cases and controls. A significantly reduced risk for ovarian cancer was seen in women who had undergone these procedures, particularly if they were performed at younger ages. Data from a case-control study in Washington, DC, demonstrated a 30% risk reduction in women undergoing hysterectomy with preservation of the ovaries.[28] Similarly, a case-control study performed in Japan, where incidence of ovarian cancer is low, found that a significantly lower proportion of ovarian cancer patients than controls had undergone permanent sterilization.[48] Of note is the observation by Cattanach of decreased estrogen excretion in women who had undergone tubal ligation, a finding that he suggested may be related to localized procedure-induced vascular changes.[7]

Two alternative hypotheses have been advanced to explain the findings related to reproductive history that were described previously. One theory, first proposed by Fathalla,[20] contends that constant, uninterrupted ovulation leads to an increased risk for ovarian cancer by virtue of the repetitive trauma to the ovarian epithelium and resultant cellular proliferation associated with the ovulatory cycle, the potential for entrapment and transformation of epithelial inclusion cysts, or the repetitive exposure of the epithelium to steroid-rich follicular fluid or pituitary gonadotropins.[14, 76] Thus, events such as pregnancy and OCP use, which suppress ovulation, would decrease this risk. A number of investigators have actually calculated measures of duration of ovulation by subtracting anovulatory time during pregnancy and lactation and while taking OCPs from time at risk for ovulation, and found a significant correlation

Table 1. RELATIVE RISK OF OVARIAN CANCER BY ORAL CONTRACEPTIVE USE

Reference (No.)	Cases/Controls		Relative Risk Estimate (95% Confidence Interval)
	Users	Nonusers	
CDC[8]	197/439	2335/3867	0.6 (0.4–0.9)
Weiss[71]	21/112	207/552	0 57 (0.05–1.92)
Rosenberg[59]	33/136	187/539	0.6 (0.4–0.9)
Wu[76]	188/299	619/1011	0.74 (0.52–1.06)
Cramer[11]	34/144	48/139	0.38 (0.15–0.96)
Harlow[27]	66/194	82/193	0.7 (0.4–1.2)
LaVecchia[37]	39/178	367/1104	0.68 (0.48–0.97)

between ovarian cancer risk and duration of ovulation.[6, 76] Support for this theory also comes from a little-known experiment in which epithelial ovarian cancers were induced in hens by using prolonged fluorescent lighting to induce ovulation and maximize egg production.[75]

The alternative hypothesis contends that nulliparity, rather than failing to offer protection against ovarian cancer, is actually a manifestation of an underlying reproductive disorder, which also predisposes to the development of the malignancy. At least four case-control studies have found a significantly increased prevalence of infertility among cases as compared with controls, whether infertility is measured by self-reporting of difficulty in conceiving,[33, 46, 74] physician-diagnosed infertility,[74] or number of years of unprotected intercourse without conception.[46, 49] Incidence of abortion, stillbirth, and congenital malformation do not appear, however, to be related to ovarian cancer risk.[46, 48] A role for altered pituitary gonadotropin levels, which may be the basis for subfertility in many women, is supported by the epidemiologic observation that incidence rates for ovarian cancer accelerate around the time of menopause, when gonadotropin levels also show a sharp rise.[23, 64] It is also consistent with the previously described apparent protection afforded by OCP use, which is associated with suppression of pituitary gonadotropins.[9] In fact, a case-control study performed by Harlow et al[27] described an interactive effect between high lactose intake and the protection afforded by oral contraceptive use. They propose that it is in the setting of a hypergonadotropic state induced by high galactose levels that OCPs exert their protective, gonadotropin-lowering effect. The altered gonadotropin theory is also consistent with the observed reduction in risk following sterilization procedures, which have been shown to alter ovarian blood flow and hormonal activity.[1, 58] There are also some data from murine models in which elevated gonadotropin levels are associated with ovarian tumor promotion, but the applicability of this model to human carcinogenesis is questionable.[61]

SUMMARY

The epidemiologic data collected to date have provided some important and provocative clues as to the etiology of ovarian cancer. The recognition of familial clustering of this disease has led to exciting advances in understanding the genetics involved. The contribution of endocrine factors has been well documented in the epidemiologic literature, leading to important insights into the process of carcinogenesis. Clearly, additional information is needed to further explain the interplay of genetic, physiologic, and life style factors, to lead to a better understanding of the disease, and ultimately to a means of prevention and control.

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PATHOLOGY EPITHELIAL TUMO

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This article reviews the pathology of epithelial tumors of the ovary particular emphasis on newer information in the literature. Most discussion is devoted to the most common category of malignant tumors, which have usually been referred to in recent years as "co epithelial" or "surface epithelial" cancers.[46, 47] These are designated " epithelial-stromal tumors" in the revised classification of ovarian tumors World Health Organization (WHO) (Table 1) that is currently being fi Also discussed briefly is a recently described highly malignant epithelial that does not appear to belong in this category, but that is import oncologists to recognize, the small cell carcinoma.[14] Although almost types of surface epithelial-stromal tumor include those of borderline nancy, those of endometrioid,[3, 38, 50] clear cell,[4, 40] and transitional cell[21] are rare and will not be discussed. Some particularly important probl differential diagnosis of epithelial cancers of which the clinician sh aware will be mentioned; these problems have been discussed in great elsewhere, along with others.[60]

Surface epithelial-stromal tumors account for approximately two th all ovarian neoplasms, and their malignant forms for about 90% of cancers.[46] In the designation given to a neoplasm in this category, criteria are considered. The two most important are the cell type, i.e., mucinous, and so on—and whether the tumor is benign, of so-called bo malignancy, or frankly malignant. The final two criteria are architectu pertains to whether the tumor is exophytic, endophytic, or both exophytic growth is present, the word "surface" is added to the desi e.g., serous surface papillary carcinoma. The second relates to the proportions of the epithelial and stromal components of the neoplas surface epithelial-stromal tumors are predominantly epithelial, with minor portion derived from the ovarian stroma; when a tumor has a p

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