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Memorandum

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E. EDWARD KAVANAUGH
PRESIDENT

TO: Talc Interested Party Task Force

FROM: Carol J. Eisenmann, Ph.D., Research Associate

DATE: July 23, 1998

SUBJECT: Daly M, Obrams GI. 1998. Epidemiology and risk assessment for ovarian cancer. Seminars in Oncology 25(3):255-264.

In this paper, the Wehner (1994) paper (reference 36, page 258) is cited as "some data indicate that talc may be transported retrograde through the fallopian tubes to the ovaries" - which was not the conclusion of the Wehner paper.

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Epidemiology and Risk Assessment for Ovarian Cancer

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The incidence of ovarian cancer varies internationally with higher rates among women of North America and northern Europe. In the United States, there has been relatively little change in the incidence of ovarian cancer in recent decades. The incidence rate of ovarian cancer is highest among white and Hawaiian women, intermediate among African-American, Hispanic and Asian-American women, and lowest among Native American women. The most intensively studied risk factors have been family history, pregnancy history, and oral contraceptive use. Multiparity, lactation, oral contraceptive use, and tubal ligation/hysterectomy all decrease a woman's risk of ovarian cancer. One exposure that has been consistently associated with increased ovarian cancer risk is cosmetic talc applied to the perineum.

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OVARIAN CANCER ranks second among gynecologic cancers in incidence among the major types of cancer in women in the United States, with 25,400 cases estimated for 1998, and ranks first in overall mortality from gynecologic cancers, with 14,500 deaths estimated for 1998.[1] Ovarian cancer is a highly lethal disease with an insidious onset; while it accounts for 4% of all cancer incidence among women, it is the fifth leading cause of cancer death. Thus, ovarian cancer is of great interest and importance to cancer researchers, and there are some intriguing leads in etiology and prevention.

HISTOPATHOLOGY

The most common type is epithelial ovarian cancer (90% of malignant ovarian tumors), which originates from cells of the surface germinal epithelium of the ovary. Coelomic epithelium can differentiate into serous, ciliated columnar cells (such as in the fallopian tubes), or mucinous, nonciliated columnar cells (such as in the endometrium). Epithelial ovarian tumors may thus take various forms, with serous, mucinous, and endometrioid being the most common classifications.

The nonepithelial types of ovarian cancer are the sex cord-stromal tumors (6% of malignant ovarian tumors), germ cell tumors (3%), and indeterminate tumors (1%). Most recent research has focused on etiologic differences between the pathologic subgroups of ovarian cancer.

A type of ovarian cancer variously called low malignant potential or borderline is characterized by good prognosis and may be analogous to *in situ* tumors of other organ sites.

DESCRIPTIVE EPIDEMIOLOGY

International Distribution

Few cancers show as wide a variation in incidence rates as does ovarian cancer. In general, the high-risk countries include the industrialized countries, especially North America and northern Europe, with the notable exception of Japan. The highest rates are observed in the Scandinavian countries, Israel, and North America. The lowest rates are observed in developing countries and Japan. When women move from areas with a low incidence of ovarian cancer to higher risk areas, their descendants' risk approaches that of native-born women within a few generations.

A study of ovarian cancer mortality among numerous immigrant groups in Australia and Canada showed gradual convergence with local mortality rates. The convergence of rates of immigrants from low-risk countries may be explained by lower fertility than in the country of origin, as well as lower usage of oral contraceptives (OCs) than among native-born women.[2]

Incidence and Mortality

The 1987-1991 age-adjusted incidence was 14.8 cases per 100,000 American women.[3] As with many types of cancer, ovarian cancer is a disease of increasing age. Epithelial ovarian cancer is uncommon in women younger than the age of 40 years, after which incidence rates increase sharply until the eighth decade of life, then decrease slightly. The age-specific incidence rates in-

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crease from 2 to 3 cases per 100,000 in the third decade to 59 cases per 100,000 in the eighth decade.[3]

Ovarian cancer is highly fatal; more than 75% of cases are diagnosed with advanced disease and current survival rates are poor. The mortality rate from ovarian cancer increased with each successive cohort born after 1861, peaked among women born in the early 1900s, and has slowly decreased with each successive generation.[4] The increasing trend in mortality from ovarian cancer has slowed since the 1970s, decreasing 7% in the last two decades, mainly among women younger than 55 years of age and coincident with the use of OCs.

Race Distribution

In the United States, the incidence rate for ovarian cancer is significantly higher among white and Hawaiian women, intermediate among African-American, Hispanic, and Asian-American women, and lowest among Native American women. Presumably, this reflects differences in the distribution of risk factors. From 1986-1990, the incidence rate among whites was 50% higher than among African-Americans, observed in both premenopausal and postmenopausal women.[3] Both white and African-American women have a similar age pattern of incidence, and the known risk factors appear to operate similarly in both groups.[5]

Time Trends

In high-risk countries such as the United States, there has been little change in the incidence rate of ovarian cancer during the last three decades, with only a slight increase especially in the oldest age groups. A trend of increasing incidence has been reported in previously low-risk countries.

ANALYTIC EPIDEMIOLOGY

Analytic epidemiologic studies have examined a number of potential risk factors for ovarian cancer. The emphasis is on identifying modifiable risk factors, creating possibilities for primary prevention, and on identifying women at high risk who are thus candidates for screening and early detection. Among these factors, the ones that have received the most attention relate to reproductive factors.

Epidemiologic studies have led to three theories regarding the etiology of ovarian cancer: (1) continuous uninterrupted cell division and regeneration of ovarian epithelium with each ovulation provides opportunity for mutation and malignant transformation; (2) pituitary gonadotropin stimulation leads to malignant transformation; and (3) the ovary is exposed to carcinogens that can travel to the ovary via the vagina and fallopian tubes. These hypotheses are not mutually exclusive, and different effects may predominate at different ages, especially premenopausally versus postmenopausally.

Multiparity, lactation, and OC use all decrease a woman's risk for ovarian cancer. In data combined from 12 United States case-control studies of epithelial ovarian cancer, the estimated risk of developing ovarian cancer before age 65 for the total population is 0.8%. Among women with no family history of ovarian cancer, the lifetime risk varies from 0.6% among those with three or more term pregnancies and 4 or more years of OC use, to 3.4% among nulliparas with no OC use. Among women with a positive family history, the lifetime risk of developing ovarian cancer is estimated as 9.4%.[6]

Parity

Women who are multiparas have a 30% reduction in ovarian cancer risk compared with nulliparas. In a large prospective study, parity was the only reproductive factor that had a substantial independent association with ovarian cancer; parous women had a 45% decrease in ovarian cancer risk relative to nulliparous women, regardless of age at first birth; each birth was associated with a 16% decrease in risk.[7] Other studies confirm the trend: Hartge et al note that each additional pregnancy decreases a woman's ovarian cancer risk by 10% to 15%[6]; Adami et al note that each additional birth decreases a woman's ovarian cancer risk by 14% to 22%.[8]

In case-control studies, incomplete pregnancies, due either to a spontaneous or induced abortion, either decrease risk slightly or are not associated with ovarian cancer risk in either nulliparous or parous women.[9,10] In contrast to the protective effect of pregnancy, most studies do not show any significant effects of age at menarche, age at first birth, or age at menopause with regard to ovarian cancer risk.[8]

Infertility and Fertility Drug Use

Increased ovarian cancer risk among nulliparas could reflect an association between ovarian cancer and infertility. Childless women who have been pregnant have the same risk as nullipars.[11] In a pooled analysis of studies of ovarian cancer, ovarian cancer risk was increased among women who had used fertility drugs, with an odds ratio of 4.0 among women with low malignant potential tumors and 2.8 among women with invasive ovarian cancer, with the highest odds ratio (27.0) for nulliparas with infertility drug use.[12] In a case-control study from Italy, and a record linkage study in Denmark, no such associations were found, although the numbers were small.[8,13] Infertile women who have taken clomiphene for 12 or more ovulatory cycles have been reported to be at greater risk of ovarian cancer than infertile women who haven taken it for less than 1 year or not at all; no excess risk is associated with the use of human chorionic gonadotropin.[14]

Pelvic inflammatory disease (PID) may result in

infertility and may stimulate proliferation of surface epithelium of the ovary. In a case-control study, a self-reported history of PID, adjusted for age, parity, OC use, and other factors, was associated with an odds ratio of 1.5 with ovarian cancer. Higher risk was found among women with recurrent PID, younger women, women with parity 0 or 1, infertile women, and women who had PID before age 20.[15]

Lactation

Women with a history of lactation have a lower risk of ovarian cancer than women who have not breast-fed. Lactation is known to suppress ovulation in some women. Whittemore et al reported that ovarian cancer risk decreases almost 1% for each month of lactation. The protective effect is strongest in the months immediately after delivery—when ovulation is most likely to be suppressed.[11] Pregnancies with lactation appear to be slightly more protective than pregnancies without; the inverse association was stronger for more average months of lactation per pregnancy.[10]

Exogenous Hormones

Combined OCs have been shown to reduce risk of ovarian cancer, and their protective effect is one of the best established findings in the epidemiology of ovarian cancer. The use of OCs appears to decrease a woman's risk of ovarian cancer by 30% to 60%, depending on the duration of use. In the Oxford Family Planning Association cohort study, the relative risk of ovarian cancer for OC users was 0.4; in comparison with never users, the relative risk for up to 48 months of OC use was 1.0, while the relative risk for OC use of 97 months or longer was 0.3.[16] The risk of epithelial ovarian cancer decreases with increasing duration of OC use; Hankinson et al estimated that risk decreases 11% with each year of OC use; however, little additional protection from 6 or more years of use is observed. The protective effect among nulliparous and multiparous users is similar.[7] Data suggest that early formulations of OCs provide enhanced protection; women who have terminated use for 15 or more years are at lower risk than are recent OC users.[11]

To determine the effect of OC use on the cumulative incidence of epithelial ovarian cancer, an analysis of the Cancer and Steroid Hormone Study data was conducted.[17] The results suggested that 5 years of OC use by nulliparous women can reduce their ovarian cancer risk to that of parous women, and that 10 years of OC use by women with a positive family history can reduce their risk to a level below that of women with a negative family history.

Gonadotropin stimulation may be an etiologic factor in ovarian cancer. Use of exogenous estrogens, hormone replacement therapy (HRT), which may reduce the high gonadotropin levels of postmenopausal women, could decrease ovarian cancer risk. While a few studies have reported such a reduction, and a few show a positive association,[18] the majority of studies have not observed a relationship between HRT and ovarian cancer.[19,20] Progestational postmenopausal agents have been in use for too short a time to provide an assessment of their relationship to ovarian cancer risk.

In a study of women younger than 55 years, ovarian cancer was found to be increased 2.5-fold in women with polycystic ovarian syndrome (a condition associated with increased levels of luteinizing hormone [LH] and adrenal androgens). The association was found to be stronger in women who never used OCs (odds ratio 10.5) and women who were very lean at age 18 (odds ratio 15.6).[21] The use of OCs also decreases the LH: follicle stimulating hormone (FSH) ratio in women with polycystic ovarian syndrome to levels found in other OC users.

Endogenous Hormones

A nested case-control study of serum gonadotropins and steroid hormones has shown that women with low serum gonadotropin (FSH and LH) levels are at increased risk of ovarian cancer, as are women with high androgen levels. Specifically, higher androstenedione levels and dehydroepiandrosterone (DHEA) levels are associated with increased risk. The risk of ovarian cancer increases with increasing levels of these hormones. Replication of these findings is a matter of some urgency since DHEA is being sold over-the-counter for nonmedical "health" uses. These findings do not support the hypothesis that gonadotropin stimulation is an etiologic factor in ovarian cancer.[22] Instead, OCs and gonadotropins may act through changing androgen levels: OCs suppress gonadotropins, in turn, the ovary produces less androgens, estrogens, and progesterone. It is also important to consider that the levels of steroids in follicular fluid and the ovarian epithelial microenvironment may be far more important in ovarian cancer pathogenesis than are serum hormone levels, which are what we generally measure.

A cohort study of women with endometriosis, who may experience various hormonal and/or immunologic abnormalities, showed a relative risk of ovarian cancer of 4.2 in women with long-standing disease.[23]

A recent molecular epidemiologic study suggests that women who have more total ovulatory cycles in their lifetime (calculated as 13 cycles per year between menarche and menopause minus the time spent on OCs, pregnant, or lactating) are at higher risk of having p53-positive tumors if they develop ovarian cancer. As a result of the increased cell division at the time of ovulation, a higher number of ovulatory cycles may lead to increased DNA damage.[24] Another study conducted in Mexico also concludes that the estimated number of

ovulatory cycles shows a direct and highly significant association with ovarian cancer.[25]

The etiology of ovarian cancer may be heterogeneous. Among younger women exposed to fewer ovarian cycles, aside from familial predisposition, exposure to androgens may play an important role in etiology. Among older women exposed to a greater number of cycles, continuous uninterrupted ovulation may be the more important factor.

Previous Tubal Ligation or Hysterectomy

Tubal ligation and/or hysterectomy physically interrupts the utero-ovarian circulation, but no consistent reports of changes in estrogen secretion after such surgery have been reported. Others[26] have proposed that there are growth factors, possibly including insulin growth factor I, epidermal growth factor, or colony stimulating factor I, secreted by the uterine stroma or smooth muscle that are decreased after surgery. Certainly, the route from the vagina through the uterus to the ovary is interrupted by gynecologic surgical procedures, and thus exposure of the ovaries to external toxins is likely to be diminished. The hypothesis that surgery prevents exogenous agents from entering the peritoneal cavity is somewhat supported by analyses that showed that hysterectomy offered no additional protection from ovarian cancer to women who had previously undergone tubal ligation.[11]

Case-control and record linkage studies have shown decreased risks of ovarian cancer after tubal ligation and/or hysterectomy.[26-29] A case-control study of ovarian cancer in a very low-risk country, India, that has a high rate of childbearing and early age at first pregnancy and where tubal ligation is widely practiced, the only significant factor to influence ovarian cancer risk was tubal ligation, with an odds ratio of 0.25.[30] A large prospective study found a strong inverse correlation between tubal ligation and subsequent ovarian carcinoma, adjusted for known risk factors.[7] One case-control study showed a significant odds ratio of 0.5 of ovarian cancer after hysterectomy; no difference was seen in risk according to years since hysterectomy.[10] The protective effect of these surgical procedures appears to decrease only 20 or 25 years after surgery.

Data regarding the effect of younger or older age at surgery is inconsistent, as is the data on whether protection is greater for clear cell/endometrioid or mucinous ovarian tumors. If estrogen exposure were to increase risk for the most estrogen-responsive tumors, the clear cell/endometrioid types, then it can be hypothesized that tubal ligation or hysterectomy decreases the exposure of the ovaries to estrogen by decreasing the production of hormones by the ovary by decreasing blood supply. If surgery were to provide early diagnosis and treatment of premalignant conditions, as has been suggested, then the protective effect of surgical procedures should wane with time since surgery, but this has not been seen in the majority of studies.

Subsites/Premalignant Conditions

In a case-control study of epithelial ovarian tumors comparing risk factors for nonmucinous tumors to mucinous tumors, it appears that mucinous ovarian tumors may be etiologically unrelated to other types of epithelial tumors.[31] The benefit of OCs appears to hold true only for epithelial (but not mucinous) tumors of the ovary that share reproductive risk factors with endometrial. The protective effect of pregnancy does not hold for mucinous tumors; in one case-control study, while for each full-term pregnancy the odds ratio of ovarian cancer was 0.76 for non-mucinous tumors, for mucinous tumors it was 1.03. Mucinous tumors should be considered a distinct etiologic entity separate from the epithelial neoplasms.

Borderline neoplasms seem to share many of the same risk factors as invasive cancers.[12,32]

A case-control study of risk factors for benign ovarian teratomas showed that patients tended to be better educated and report a history of infertility. No clear relationships were found with parity, age at menarche, menstrual pattern, menopausal status, abortions, age at first pregnancy, or OC use.[33]

In a pooled case-control study of nonepithelial ovarian tumors for germ cell tumors in adults, risk was increased by OC use, higher teenage weight, and incomplete pregnancies, and decreased by parity. No association was seen with age at menarche, age at first pregnancy, or duration of lactation. Regarding stromal tumors, risk was increased by term pregnancy, incomplete pregnancy, increased age at first pregnancy, and decreased by OC or HRT use; no association was seen with duration of lactation, age at menarche, age at menopause, hysterectomy, or tubal ligation.[34]

Talc

The use of cosmetic talc in dusting the perineum, in feminine hygiene sprays, or on sanitary napkins, condoms or diaphragms has been suggested as a possible risk factor for ovarian cancer. Studies of women undergoing laparoscopy suggest that the majority of women have retrograde menstruation[35]; some data indicate that talc may be transported retrograde through the fallopian tubes to the ovaries.[36] In a case-control study, a significant odds ratio of 1.5 was reported for use of talc, with higher risks in those women who applied it directly to the body, on a daily basis, or for more than 10 years.[37] Three case-control studies found that in contrast to talc used on the perineum, talc used on diaphragms and condoms is not associated with increased ovarian cancer risk.[38-40]

Talc was contaminated with significant amounts of asbestos.[38] This has led to research on women asbestos workers, and several investigators report an increased risk of ovarian cancer in these cohorts.[41] A recent small study designed to investigate whether asbestos could be detected in the ovaries of women with household asbestos exposure (husbands or fathers in asbestos industries) showed that asbestos fiber can be found in the ovaries of the majority of women with household exposure, and that fiber burdens were higher in those with exposure histories.[41]

Dietary Factors and Physical Activity

Galactose metabolism has been proposed as a risk factor for ovarian cancer based on data that galactose is toxic to oocytes: galactosemic women have premature menopause and increased gonadotropin levels. In a study of women with ovarian cancer with a family history of ovarian cancer, compared with controls without a family history of ovarian cancer, the mean activity of erythrocyte galactose-1-phosphate uridyl transferase (a key enzyme in galactose metabolism) is significantly lower among the cases.[42] Another case-control study of dietary lactose intake (adjusted for age, number of pregnancies, OC use, and caloric intake) showed no association between average daily consumption of lactose or galactose, or history of lactose intolerance, and ovarian cancer risk.[43] A case-control study focusing on galactose intake and metabolism (adjusted for age, number of pregnancies, OC use, caloric intake, duration of lactation, hysterectomy, and age at menopause) found no associations between lactose or galactose intake, intestinal lactase activity, or mean erythrocyte galactose-1-phosphate uridyl transferase and ovarian cancer risk.[44] The investigators speculate that a possible reason for the difference between their results and those of Cramer may be due to the impact of systemic cancer treatment of cases in the earlier study.

Brassica vegetables (including cabbage, kale, broccoli, Brussels sprouts, cauliflower, turnip and rutabaga) have been studied for their potential protective effect against various cancers, but no consistent protective effect for ovarian cancer has been found to date.[45]

In a nested case-control study, women in the upper three quartiles of waist-to-hip ratio were at two-fold higher risk of ovarian cancer, without evidence of a dose response relationship. In contrast, women who reported regular leisure physical activity had a 1.5-fold greater risk, and women who engaged in vigorous physical activity more than four times a week had a 2.5-fold greater risk.[46] In a case-control study in Australia, women with a body mass index (BMI) greater than the 85th percentile had approximately double the cancer risk of women in the middle 30% of the BMI range; the trend of increasing cancer risk with BMI remained significant in multivariate analysis.[47] Because a high waist-to-hip ratio can be associated with hyperandrogenemia and polycystic ovary syndrome these factors may be responsible for the increase in risk. Regular strenuous exercise increases the number of anovulatory cycles, which should actually be protective for ovarian cancer; however, a negative effect of vigorous physical activity on circulating estrogens may, by feedback, increase serum gonadotropins.

In England, there is a geographic association between tall stature and ovarian cancer; in a nested case-control study women who developed ovarian cancer were found to have gained significantly more weight during the first year of life than controls; leading the investigators to speculate that patterns of gonadotropin release established *in utero* are linked to both weight gain and subsequent ovarian cancer.[48]

Other Risk Factors

In a record-linkage study of women employed in hairdressing in four Nordic countries, a small increased risk for ovarian cancer incidence was reported.[49] The increase was significant only in Finland with a standardized incidence ratio of 1.88. This preliminary finding may be of further interest because hair dyes contain known mutagens.

In a reanalysis of two case-control studies, focused on self-reported medication use and ovarian cancer, an adjusted odds ratio of 1.8 was found for use of antidepressants or benzodiazepine tranquilizers, primarily among women whose first use occurred before age 50 (odds ratio 3.5). The investigators speculate that this finding may be related to induction of hepatic microsomal enzymes, as shown in earlier studies of exposure to tricyclics and benzodiazepines, or a tumor promoting effect.[50]

No association between smoking and ovarian cancer has been observed.[11,51,52]

While insulin resistance may coexist with hyperestrogenism and hyperandrogenism, a case-control study focusing on diabetes and ovarian cancer found no relationship between the two illnesses, adjusted for age, body mass, race, OC use, or parity.[53]

GENETIC EPIDEMIOLOGY

Among the factors associated with ovarian cancer, none alters the magnitude of risk more than a family history of the disease. The familial aggregation of ovarian cancer has been shown in numerous case series and case-control studies. These studies have illustrated statistically significant increases not only in ovarian cancer, but also breast, endometrium, and colon cancers among relatives of women with a primary ovarian cancer.[54] Schildkraut and Thompson used data from the Cancer and Steroid Hormone Study to estimate an odds ratio for ovarian cancer of 3.6 in first-degree relatives,

and 2.9 in second-degree relatives of women with a primary ovarian cancer. An excess of affected relatives was seen in both maternal and paternal lines. The odds ratio for mothers of cases was three times that of sisters of cases, lending support to the likelihood of an autosomal dominant mode of inheritance. Relatives of breast cancer probands also had an increased risk for ovarian cancer.[55] Lending further support to a proposed genetic mechanism for ovarian cancer is the occurrence of both breast and ovarian cancer in the same woman. Data from the Birmingham Cancer Registry in England found a significant excess of second primaries in premenopausal women with either breast or ovarian cancer. Greggi et al[56] report a five-fold increase in rates of breast cancer occurring as a second primary among familial ovarian cancer cases, as compared with sporadic ovarian cases.

The observation of familial patterns of ovarian cancer has prompted attempts to evaluate the genetic features of ovarian tumors. Cytogenetic characterization of surgical specimens from ovarian tumors has revealed extensive and complex structural chromosome abnormalities involving chromosomes 1, 3, 6, 11, 14, and 17.[57-61] Multiple sites of loss of heterozygosity (LOH) have been observed frequently in ovarian tumors and cell lines derived from tumor specimens. Both allelic loss and mutations of p53 are observed at all stages of ovarian cancer and do not correlate with prognosis.[60,62] The predominance of transition mutations seen in p53 suggests that they arise from spontaneous errors in DNA synthesis rather than exposure to environmental carcinogens.[63]

The frequent observation of LOH on one or more loci of the long arm of chromosome 17[64] suggested the possibility of a tumor suppressor gene on that chromosome. Linkage studies within families with both site-specific ovarian and breast-ovarian cancer patterns strengthened the assignment of a breast-ovarian cancer susceptibility locus, termed BRCA1, to the long arm of chromosome 17.[54,65] A study of allelic loss in tumors from four multiple-case breast-ovarian cancer families linked to the BRCA1 locus demonstrated loss of the remaining wild-type allele in each tumor tested, thus providing strong evidence that BRCA1 is a tumor suppressor gene.[66]

In 1994 the BRCA1 gene was identified by positional cloning and found to encode a protein of 1863 amino acids. More than 100 mutations in the gene have been described, many of which result in premature truncation of protein transcription.[67] A second breast cancer susceptibility gene, BRCA2, was localized through linkage studies to the long arm of chromosome 13. In addition to accounting for 35% of hereditary breast cancer, it is also associated with male breast cancer, ovarian cancer, prostate cancer, and pancreatic cancer.[68,69] Finally, LOH studies have identified a locus distal to BRCA1 on chromosome 17 in both familial and sporadic ovarian tumors, suggesting an additional gene locus.[70]

Hereditary ovarian cancer is thought to account for 5% to 10% of all ovarian cancer. Since the identification and cloning of the BRCA1 and BRCA2 genes, research has focused on studies to understand the functions of the gene products, their population frequencies, gene penetrance, the clinical implications of mutations carrier status, and the potential gene-environment interactions which may affect their expressivity. Estimates of the gene frequency of BRCA1 and its contribution to ovarian cancer incidence vary widely. On the basis of two population-based genetic epidemiology studies, Ford et al[71] estimate a gene frequency of BRCA1 in the general population of 0.04% to 0.20%. This estimate varies widely by country of origin, however. Certain of the BRCA1/2 mutations are found in much higher frequency in Ashkenazi Jews. Among a sample of more than 5,000 individuals in Washington, DC, 2.3% tested positive for one of the three mutations common among Ashkenazi Jews, the 185delAG and 5382insC mutations in BRCA1, and the 6174delT mutation in BRCA. Carrier frequencies were highest for affected females who were younger than 50 years at diagnosis (14%). The frequencies for men and women without any personal or family history of cancer was 1.3% and 1.2%, respectively.[72]

On an international scale, BRCA1 mutations are most common in Russia, occurring in 79% of high-risk families, with two common alleles accounting for the majority of mutations. In contrast, in Italy where 29% of high-risk families are mutation carriers, there are many unique mutations, indicating multiple founders.[73] Another mutation in BRCA2, 999del5, has a high prevalence of 0.4% in the Icelandic population.[74] The phenotype of this mutation includes both early onset breast cancer and ovarian cancer.

While it is clear that female carriers of BRCA1/2 mutations are at significantly increased risk of breast and ovarian cancer, precise estimates of gene penetrance also vary widely, due at least in part to differences in populations studied and study designs. Using data from families with evidence of linkage to BRCA1, Easton et al[75] estimated a lifetime risk of ovarian cancer of 63%. In the Washington study among Ashkenazi Jews, where only three mutations were assessed, the risk of ovarian cancer among mutation carriers was 16% by age 70.[72] The highest risk for ovarian cancer was observed among carriers of the 5382insC mutation, and the lowest for the 185delAG mutation. In a case series reported from Jerusalem, however, no ovarian cancer cases carried the 5382insC mutation.[76] The expression of ovarian cancer was notably lower in carriers of mutations of BRCA2 compared to carriers of BRCA1 mutations among cases in another study from Israel.[77]

Differential expression of ovarian cancer by site of

mutation has been a subject of considerable interest. Gayther et al[78] have observed a significant correlation between location of BRCA1 mutations near the 5′ end of the gene and an increased proportion of ovarian cancer. While this observation is supported by in vitro studies showing that ovarian cancer cell growth is not inhibited by mutations in the 5′ portion of the gene, but is inhibited by 3′ BRCA1 mutations,[79] Peelen et al[80] were unable to assign a specific phenotype to any of the common BRCA1 mutations in a series of Dutch and Belgian breast and ovarian cancer patients, and data from the Jerusalem series showed an opposite trend for increased rates of ovarian cancer with mutations at the 3′ end.[77] In BRCA2, mutations in exon 11, termed the ovarian cancer cluster region, have been reported to be associated with ovarian cancer in one series.[69]

A consensus appears to be emerging that hereditary ovarian cancer, similar to hereditary breast cancer, is characterized by an earlier age at onset. Henry Lynch reports a significantly lower age at onset for familial ovarian cancer (52 years) than that in the general population (59 years).[81] A recent report from the Gilda Radner Registry found age at diagnosis among multicase families to be up to 10 years earlier than cases reported to Surveillance, Epidemiology, and End Results program registries.[82] A similar age differential has been observed in a series of cases in Israel.[83] Data from the Gilda Radner Registry also suggest a significant trend for earlier age at diagnosis of ovarian cancer with successive generations in hereditary ovarian cancer, a phenomenon known as "anticipation." Although no plausible biologic explanation currently exists to explain this observation, further research is warranted to elucidate potential new biologic mechanisms.

Characterization of the clinical course of hereditary ovarian cancer will have important implications for therapeutic management. The majority of BRCA1-related ovarian cancers are predominantly serous. Ovarian tumors of low malignant potential are rarely reported in hereditary breast-ovarian families, and it is unclear if they are part of the BRCA1 phenotype.[84] There are now two series reporting prolonged survival in BRCA1 related cancers,[85,86] although methodologic limitations qualify interpretation of these findings.

Finally, basic research on the function and expression of the BRCA1/2 genes may ultimately have significant bearing on preventive and treatment approaches to hereditary ovarian cancer. The recent discovery in mice of an interaction between the BRCA genes and HsRad 51, a DNA-repair protein, suggests that the protein complex formed plays a key role in resolving double-stranded DNA breaks. The additional finding that both BRCA2 and Rad knockout mice exhibit hypersensitivity to γ-irradiation provides a potential molecular model of gene-environment interaction which can be applied to our understanding of the early onset phenotype of hereditary ovarian cancer.[87] The finding of surface epithelial irregularities, including clefts, invaginations, small papillary excresences and superficial inclusion cysts in ovaries removed from high risk women for prophylaxis may provide a histopathologic marker of premalignant change.[88,89] In addition to germline mutations associated with predisposition to breast and ovarian cancer, interest is growing in the identification of susceptibility genes which may act indirectly to alter the risk of ovarian cancer. In an effort to begin to investigate potential metabolic differences between women with ovarian cancer and controls, a small case-control study was conducted to compare the polymorphisms in microsomal epoxide hydroxylase (EPHX) gene. EPHX has been shown to be highly expressed in the ovary. The odds ratio of having ovarian cancer among women with the Tyr113His polymorphism of EPHX was 2.6. This is a high-activity genotype, and could reflect differences in metabolic activation of carcinogens, such as some polycyclic aromatic hydrocarbons.[90] This and other work will contribute to our understanding of the genetic events which result in the malignant phenotype and will help clarify the epidemiologic risk factors associated with the disease.

CURRENT RESEARCH

The interaction of familial factors, BRCA1, BRCA2, and other genes conferring potential susceptibility with known reproductive and environmental risks is an area of intense study. The specific effects of age at first birth, incomplete pregnancies (ie, spontaneous abortions, stillbirths, and ectopic pregnancies) on the risk of ovarian cancer are still being studied. The effect of tubal ligation on blood flow and transfer of substances from the uterine environment to the ovary, and the potential effect on secretion of gonadal steroids, are also subjects of continued investigation.

Other areas currently under study include:

infertility and use of specific agents to induce fertility
more detailed data collection on history of perineal talc use
dietary factors, adiposity and physical activity
HRT, especially combined estrogen-progesterone therapy
other medications
levels of circulating ovarian steroids, FSH, LH
GALT gene activity
p53 and k-ras mutations, LOH in tumor tissues
alleles of blood group substances; variations in glycolipid synthesis
tumors of borderline malignancy and subgroups of ovarian cancer by pathologic type

The ultimate goal of these efforts is to apply our understanding of the events leading to ovarian carcinogenesis to novel therapeutic and preventive approaches.

The recent identification of genes which play a critical role in the malignant transformation of ovarian epithelium not only identifies a group of women with a significantly increased risk of disease, but also provides new molecular tools to characterize the carcinogenic process and to identify potential sites for its interruption.

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