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Epidemiologic and Genetic Factors Associated with Ovarian Cancer

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Abstract

The purpose of this paper is to provide a comprehensive review of the epidemiologic and genetic factors associated with ovarian cancer. A more complete understanding of the determinants of ovarian cancer may lead to the development of better screening and detection methods for this disease. The first section of this paper reviews current literature on screening and early detection of ovarian cancer. The second section reviews the epidemiology of ovarian cancer, specifically highlighting the risk factors associated with the development of this disease. The paper concludes with a discussion of how oncology nurses can apply this information to improve patient care.

INTRODUCTION

Ovarian cancer has the highest mortality rate of all female cancers; more than 50% of the 21,650 women diagnosed with ovarian cancer die annually from this disease.[1] A more complete understanding of the epidemiologic and genetic determinants of ovarian cancer may lead to the development of better screening and detection methods for this disease. The first section of this paper reviews current literature on screening and early detection of ovarian cancer. The

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second section reviews the epidemiology of ovarian cancer, highlighting specific risk factors associated with this disease. The paper concludes with a discussion of how oncology nurses can apply this information to improve patient care.

CURRENT SCREENING AND EARLY DETECTION OF OVARIAN CANCER

Screening

There is inadequate evidence to support screening for ovarian cancer in the general population. However, two large, ongoing prospective randomized control trials (RCT)[2,3] should provide important information about the efficacy of using Transvaginal Ultrasound (TVU), CA125, and screening examinations for the early detection of ovarian cancer.

The first RCT, being conducted in the United States, is the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial, sponsored by the National Cancer Institute (NCI). This study includes 37,000 healthy postmenopausal women between 55 and 74 years of age who were randomized to either an annual CA125, TVS, and pelvic examination or standard care.[2] The endpoints are cost and the establishment of important time-points for screening. The outcome variable is mortality. Patients will be followed for 13 years. Based on preliminary analyses, 1338 participants (4.7%) had abnormal TVU and 402 participants (1.4%) had abnormal CA125 (only 34 had abnormal results on both tests).[3] Data from this RCT pertaining to the efficacy of screening is still being analyzed.

The second study, being conducted in the United Kingdom, has enrolled 200,000 postmenopausal women and is called the North Thames Ovarian Cancer Study (UKTOCS). This study is attempting to determine the sensitivity of CA125 plus TVU versus TVU alone as screening measures for ovarian cancer. Study endpoints include quality of life, morbidity, and cost.[6] Enrollment was completed in 2005, and results should be forthcoming soon. These studies should provide valuable information about the crucial time points and the optimal screening methods for ovarian cancer.

Early Detection

Early detection of ovarian cancer has been a goal of clinical research. However, the underlying biology of the disease and its vague symptom profile has rendered it difficult to diagnose at early stages. A recent consensus statement[7] jointly issued by the Gynecologic Cancer Foundation, Society of Gynecology Oncologists and the American Cancer Society identified four symptoms that are more likely to occur in women with ovarian cancer: 1) bloating, 2) pelvic or abdominal pain, 3) difficulty eating or feeling full quickly, and 4) urinary symptoms (i.e., urgency or frequency). Taken together, these symptoms are called the Ovarian Cancer Symptom Index. The release of this statement was not without controversy; the symptoms identified are common in healthy women and the survey used to identify the symptoms included in the index was not prospectively validated in a sample of healthy women.[8]

Two studies have provided evidence to support the clinical use of the Ovarian Cancer Symptom Index.[9–10] Goff and colleagues[9] used a 23-item symptom survey to develop the Ovarian Cancer Symptom Index. Using this survey, the symptoms were collapsed into a single variable if the correlation coefficient among the symptoms was ≥ 0.70.[9] Odds ratios (OR) were used to compare symptoms of different duration, frequency, and severity. Finally, logistic regression was used to determine the independent contribution of the symptoms to predict risk for ovarian cancer in a different sample of high-risk women.[9]

The Ovarian Cancer Symptom Index (OCSI) was considered positive if women reported any of the following six symptoms more than 12 times in one month but that they were not present for more than one year: pelvic/abdominal pain, increased abdominal size/bloating, and feeling

full/difficulty eating. Once the symptom index was developed, the study cohort was divided into an exploratory group and a confirmatory group to test the sensitivity and specificity of the index in the confirmatory sample. The index had a sensitivity of 56.7 to detect early stage and 79.5 to detect advanced stage ovarian cancer. The specificity of the index was 90% in women older than 50 and 86.7% in women younger than 50 years of age.

The second study[10], from the same research group, combined data from the symptom index with CA125 values to determine if it improved the sensitivity and specificity of the index. This prospective case-control study enrolled 254 healthy high-risk women (due to family history) and 75 women with ovarian cancer. Cases were defined as women scheduled for surgery for evaluation of a suspicious mass. Using methods from their previous study,[9] the investigators found that cases were more likely to be older, have elevated levels of CA125, and a positive OCSI score. Fifty-three percent of the cases had a positive symptom index score and an elevated CA125; 25.3% had only an elevated CA125; and 50% of the total group of cases and controls had a positive symptom score (which represented 10.7% of the total case group). Symptom index scores independently predicted an ovarian cancer diagnosis after adjusting for CA125 levels (i.e., (OR)= 11.51; 95% confidence interval (CI)= 4.62 to 28.66). However, when used alone, the symptom index score had a lower sensitivity than CA125 level (64% vs. 78.7%). These findings suggest that the combination of CA125 and the OCSI score improved the sensitivity of detecting ovarian cancer in women participating in a high-risk screening program.

Prevention

Two methods of primary prevention of ovarian cancer are available for high-risk populations, namely chemoprevention or risk-reducing salpingo-oophorectomy (RRSO).[11–15] Chemoprevention of ovarian cancer has not been studied independently. However, several studies designed to evaluate other outcomes, have noted decreased risk for ovarian cancer in patients taking oral contraceptives (OCPs).[11,14–17]

In a large review of 12 case-controlled studies in the United States[20], OCP use and ovarian cancer risk had an overall OR of 0.67 (95% CI= 0.37–1.2), an OR of 0.62 (95% CI= 0.24–1.6) in African-American women and an OR of 0.70 (95% CI= 0.52–0.94) in White women.[19] These data suggest that ever-users of OCPs had a decreased risk for ovarian cancer.[20] The benefit of OCP use remained in women who had used OCPs for 2 to 5 years and leveled off in women who used them for 6 years or longer. These data suggest that 5 years of OCP use confers a 50% decrease in the risk for ovarian cancer with a protective effect that remains for up to 10 years after OCP use is discontinued.[11, 20–21] The mechanism by which OCP use protects against the development of ovarian cancer is its progestin effect (i.e., decrease in the number of ovulatory events).[15,21]

RRSO is defined as the removal of ovaries in women with no documented ovarian disease or with a known increased risk for ovarian cancer.[15] Four studies[11–14] evaluated the use of RRSO in women who were at high-risk for ovarian cancer. Across these studies, RRSO decreased the risk for ovarian cancer by over 90% and for breast cancer by approximately 50% with a mean follow-up time of 5 years. While surveillance of high risk women was evaluated, surgery was considered superior for risk reduction.[13–14] Patients tended to report higher satisfaction with surgery and little anxiety or regret.[15,22] Longer term follow-up is still needed. Microscopic occult disease has been found in 10 to 15% of women with genetic predisposition for ovarian cancer, and even with negative pathology, these women are still at increased risk of primary peritoneal carcinoma.[15]

EPIDEMIOLOGY OF EPITHELIAL OVARIAN CANCER

Much of the research on ovarian cancer has focused on the epidemiology of the disease because of its high mortality rate; the lack of experimental models (ovarian cancer is rare in other ovulatory animals); the small numbers of patients impacted by the disease; and the emphasis on hereditary cases.[1,11,15] According to the National Cancer Institute (NCI), a woman without a family history of ovarian cancer has a 1 in 55 lifetime chance of developing ovarian cancer. [1] This risk increases 10-fold when known familial/hereditary conditions exist.[1,15,24]

Sporadic epithelial ovarian cancer is defined as any ovarian cancer that arises in a woman with no known family history of breast, ovarian, prostate, or colon cancer[15] and is a distinct disease from sex cord-stromal ovarian tumors and germ cell tumors, which are not discussed in this review. Hereditary ovarian cancer may be associated with different genetic defects: 1) Hereditary breast and ovarian cancer (HBOC/HOC) is attributable to a germline mutation in BRCA1 or BRCA2 and 2) Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch Syndrome is due to a germline mutation in one of several genes associated with DNA mismatch repair. [22–24]

RISK FACTORS

A number of epidemiologic studies have evaluated a variety of risk factors for ovarian cancer. To date, these risk factors include: age,[1,17,21] chronic inflammation and non-steroidal anti-inflammatory drug (NSAID) use,[25–29] diet,[30–40] ethnicity,[11, 19–20] hormone replacement therapy,[15,17–18, 65–67] hysterectomy,[18] infertility drug use,[41–45] obesity,[46–50] OCP use,[15, 17–18,21] parity (pregnancy), [11,15–17] smoking,[52–57] and talc use/asbestos exposure.[58–62] The following sections summarize published data on these risk factors for ovarian cancer.

Age

Age as a risk factor for ovarian cancer, needs to be placed within the context of other events in a woman's life. Over all, age is considered a risk factor because ovarian cancer is a disease of older women. The annual incidence of ovarian cancer worldwide, regardless of age, is 42 cases per 100,000.[63] The annual incidence of ovarian cancer in women between the ages of 75 and 79 in the United States (US) is 61.3 per 100,000, higher than any other age group, when age is considered independent of all other risk factors.[1] When all other risk factors are considered, incidence is highest in women between the ages of 60 and 64.[63]

Age at menarche is considered a weak predictor of ovarian cancer risk. A moderate increase in risk for ovarian cancer occurs in women when menarche begins earlier than age 12.[1,17] No association was found when menarche begins after age 16.[17,21] Age at natural menopause has been studied. Positive associations were found with late age of natural menopause and risk for ovarian cancer.[16–18] Odds ratios for late natural menopause were reported as low as 1.19 and as high as 1.25 (95% CI=0.95–1.49).[1,17] The ratios did not achieve statistical significance, but late natural menopause was associated with increased risk for ovarian cancer.

Recently, maternal age at last birth was implicated in decreasing the risk of ovarian cancer if the last birth was at age 35 or greater.[17] This finding is important because it compared nulliparous (never pregnant) women with women who had late first time live births. These findings suggest that regardless of age at first birth, pregnancy still confers a significant risk reduction for the development of ovarian cancer. The protective effects of pregnancy may be associated with decreased in ovulation associated with higher levels of progestins.

Chronic Inflammation and Non-Steroidal Anti-Inflammatory Drugs

Chronic inflammation caused by talc and/or asbestos is a known risk factor for ovarian cancer.[25] In addition, patients with ovarian cancer have a higher incidence of endometriosis and pelvic inflammatory disease (PID).[15,21] These inflammatory processes may contribute to the development of ovarian cancer through a variety of mechanisms. Much of the available data on inflammation and cancer come from studies that evaluated the effect of non-steroidal anti-inflammatory drugs (NSAIDs) on cancer risk.[25–29]

NSAIDs have strong anti-carcinogenic effects and experimental evidence suggests that NSAIDs can impact the tumorigenic pathways in cancers of the small and large bowel.[27] Four studies examined the relationship between aspirin use and ovarian cancer.[26–29] In three[26–27,29] of the four studies, as aspirin use increased, ovarian cancer risk decreased. Mechanistically, NSAIDs have many physiologic effects. Three of these may be pertinent to the development of ovarian cancer. First, NSAIDSs interrupt the synthesis of prostaglandins, which decreases inflammation. Second, NSAIDs cause apoptosis (i.e., cell death) of human epithelial cancer cells. Finally, NSAID use may reduce the local inflammatory processes associated with endometriosis and PID.[21,29]

Data on the protective effects of NSAID use in relationship to ovarian cancer in premenopausal women is confounded by the high frequency of use of these medications in women of this age. It is difficult to determine the exact mechanisms by which NSAIDs decrease ovarian cancer risk, because NSAID use has never been measured prospectively in patients who later developed the cancer. All of the retrospective studies[26–28] had small samples and did not quantify the exact dose of NSAID used. Future research needs to clarify the role of inflammation in the development of ovarian cancer before routine use of NSAIDs as preventative agents can be recommended.

Diet

The protective effects of fruits and vegetables have been investigated in other cancers and is of interest to ovarian cancer researchers. The role of milk and other dairy products, meat consumption, fat consumption, carbohydrate intake, and alcohol use have been investigated. However, only a few studies have evaluated the impact of dietary factors on ovarian cancer risk.[30–40]

One of the first studies to examine the association between dietary factors and the risk of ovarian cancer was conducted in Northern Italy.[30] This study described the influence of red meat, alcohol, dietary fat, vegetable oil, and butter consumption on ovarian cancer risk. This case control study compared 455 patients with ovarian cancer to 1385 age-matched controls. No relationship was found between alcohol use and ovarian cancer risk. Dietary factors that increased the Relative risk (RR) for ovarian cancer included meat consumption of >7 portions versus less than 4 portions per week (RR: 1.6; 95% CI: 1.21–2.12) and butter versus fat consumption (RR 1.9; 95% CI: 1.20–3.11).[30] However, disparate measures of body weight, socioeconomic status, parity, and contraceptive use confounded these analyses. Dietary factors that decreased ovarian cancer risk included consumption of whole grain bread and pasta (RR: 0.60; 95% CI: 0.41–0.88).

A larger, cohort study[31] in the US that enrolled 29,083 post-menopausal women found that ovarian cancer risk was not associated with dietary fat intake, but did find that eggs increased the RR when consumed 2 to 4 times/week (RR: 2.04; 95% CI: 1.23–3.36).[31] This study found that green leafy vegetables were strongly associated with decreased risk for ovarian cancer (RR: 0.44; 95% CI: 0.25–0.79). No consistent association was found with meats, breads,

cereals, and starches.[31] However, this study did find statistically significant associations between increased risk for ovarian cancer and intake of sweets and dairy.

While six population-based studies[31,37–41,52] have examined the relationship between alcohol intake and ovarian cancer risk, only one found a statistically significant association.[31] However, this study showed that an intake of 10g/day of alcohol decreased the risk of ovarian cancer by 50%.[31] At the present time, no definitive conclusions can be drawn about the association between alcohol consumption and ovarian cancer risk.

Ethnicity

Few studies have reported differences in the incidence of ovarian cancer among ethnic groups primarily due to their small sample sizes. However, data from two meta-analyses [19,21] suggest that the rates of epithelial ovarian cancer are higher in white women, Odds ratio (OR) was 0.70 (95% CI: 0.52–0.94)[20] compared to black women (OR= 0.62; 95% CI: 0.24–1.6).[19] An examination of potential ethnic differences in ovarian cancer rates and other factors such as breastfeeding, oral contraceptive use, and parity, found that ethnicity explained only a small proportion of why the ovarian cancer rates were higher in white women.[19]

Ovarian cancer appears to be the only gynecologic malignancy in which race does not impact overall survival, as mortality is high across all racial groups. Ethnicity does play a role in incidence, as women of Ashkenazi Jewish descent are at greater risk for BRCA1/2 mutations, which gives them an over-representation in the numbers of hereditary ovarian cancer cases.[19]

Hormone Replacement Therapy

Several studies[30,64–65] have tried to determine whether the use of post-menopausal hormone replacement therapy (HRT) is associated with increased risk for developing ovarian cancer. However, these studies have yielded inconclusive results. Several variables need to be considered when reviewing the literature about HRT including duration of use, type of hormones, circumstances of use (e.g., surgical menopause versus natural menopause), reproductive history, and previous history of cancer in any organ.

Hormone replacement therapy is defined as any hormone orally ingested in combination (estrogen-E4 plus progesterone-P_2) or E4. Other routes of administration (i.e., creams, injections, patches) are not included in this definition, as these methods of HRT delivery have not been included in research studies that have attempted to understand HRT use and cancer risk.

It was originally thought that postmenopausal women would benefit from the supplemental use of exogenous estrogen and progesterone. Until the Women's Health Initiative[65], it was believed that the protective effects to the cardiovascular system and the prevention of bone loss outweighed the risks of HRT. However, several meta-analyses have questioned data originally used to support post-menopausal HRT use and risk for ovarian cancer.[65–67]

Hysterectomy

As previously discussed in the prophylactic oophorectomy section, hysterectomy confers a decrease in ovarian cancer risk.[24,68–69] In a large case-control study,[68] risk for ovarian cancer was decreased by 36% (RR: 0.64, 95% CI: 0.48–0.85) and tubal ligation decreased risk by 39% (RR: 0.61, 95% CI: 0.46–0.85). In high risk women, hysterectomy has also been studied, which decreases ovarian cancer risk by 50%.[15,24,69]

Infertility Drug Use

Clomiphene was approved in 1967 to treat primary infertility.[58] Several epidemiologic studies have questioned if ovarian hyperstimulation mimics "incessant ovulation" and therefore increases the risk for ovarian cancer.[41–45, 58] The use and doses of Clomiphene and the human gonadotropins (e.g., Perganol ®, Humegon ®, and Metrodin®) were not reported consistently in infertility research studies. This inconsistency in reporting makes meta-analytic procedures difficult to use to estimate the true relationship between infertility drug use and ovarian cancer. Initial studies estimated that the risk for epithelial ovarian cancer associated with the use of infertility drugs was as high as 27-fold for nulligravid women (95% CI: 2.3–315.6).[43] A subsequent, larger and more rigorous study found that the use of clomiphene resulted in a 2.3 increased risk for ovarian cancer in nulligravid women (95% CI: 0.5–11.4).[45]

Three studies[43–45] did not find an increased risk for ovarian cancer when clomiphene and gonadotropins were evaluated. These studies were rigorously designed, included an analysis of all hormonal stimulants, and followed patients through in-vitro fertilization for up to 15 years. However, a large Danish study that enrolled 684 cases and 1,721 controls, found an increased incidence of cancer in women with a history of infertility.[42] The overall odds ratio all women in the study with known fertility status for ovarian cancer was 1.54 (95% CI=1.22–1.95) The unadjusted odds ratio for ovarian cancer in infertile nuliparous women who were not treated for infertility was 3.13 (95% CI: 1.60–6.08). This 3-fold increase was observed even after adjustment for infertility treatment, drug type, and pregnancy outcome (i.e., miscarriage, induced abortion, ectopic pregnancy), where the adjusted OR was 2.71 (95% CI: 1.33–5.52).

A large retrospective, cohort study[45] was conducted to determine if a true association existed between fertility drug use and increased risk for ovarian cancer. This study enrolled 12,193 women and data included a survey of death records, registry data, historical medical records, interviews with patients, follow-up of in-vitro fertilization clinic data, and mailed surveys. The standardized incidence ratio was 1.98 (95% CI: 1.4–2.6), where women exposed to clomiphene (i.e., IR: 0.82, CI=0.4–1.5) or gonadotrophins (i.e. IR: 1.09, CI= 0.4–2.8) had a decreased risk for ovarian cancer.

Ovarian hyperstimulating drugs have been used in the US for only thirty-seven years. Therefore, many women who have used these drugs have not reached the median age of highest incidence ovarian cancer. Future studies need to follow these women throughout their menopausal experience to determine the true risk for ovarian cancer.

Obesity

Obesity is a risk factor for ovarian cancer because of its relationship to sex steroid hormones. Obesity is known to increase adrenal secretion of androgens; enhance conversion of gonadal and adrenal androgens to biologically active estrogens; and reduce sex hormone-binding globulin capacity, which increases the amount of free, biologically active estradiol.[49] Adipose tissue is the primary source of endogenous estrogens in post-menopausal women.[48–49]

Several studies have evaluated the impact of obesity on ovarian cancer risk using body mass index (BMI) as the measure of obesity. [45–49] BMI is defined as weight in kilograms divided by height in meters squared (kg/m^2). Several studies have reported a 70% increased risk for ovarian cancer in obese patients (OR: 1.7; 95% CI: 1.1–2.7).[46] However these estimates were based on cut-offs where BMI <19.8 was considered "normal" weight and BMI >24.1 was considered obese. Current guidelines from the National Heart, Lung, and Blood Institute[50] definea normal BMI to be 18.5 to 24.9 kg/m^2, overweight: 25 to 29.9 kg/m^2, obesity class 1: 30 to 34.9 kg/m^2, obesity class 2: 35 to 39.9 kg/m^2, and extreme obesity as >40 kg/m^2. In

another study using the new guidelines and a larger sample confirmed the association between obesity and increased risk for ovarian cancer at 70%.[47] In addition, obesity was associated with increased mortality in lesbian women with ovarian cancer[48].

Oral Contraceptive Use

As previously discussed, OCP use confers significant risk reduction for ovarian cancer. Other routes of hormonal contraception, including the Ortho Evra patch®, the Organon Nuva Ring®, the Mirena IUD®, and Medroxyprogesterone Acetate/Depo Provera® have not been studied in terms of risk association in ovarian cancer. Future research needs to determine if other routes of administration of hormonal contraception confer similar protective effects.

Parity

The American College of Obstetrics and Gynecology developed standardized nomenclature to refer to the pregnancy history of women. Gravidity refers to the number of times a woman was pregnant in her lifetime. Parity refers to numbers of births. Parous women have a lower risk for ovarian cancer than nulliparous women (OR=0.76; 95% CI=0.63–0.93).[15,17] Women with term pregnancies (OR= 0.87; 95% CI=0.76–0.91) versus failed pregnancies (OR=0.93; 95% CI=0.59–1.48) have a lower odds ratios, with a risk reduction of about 14% for each subsequent pregnancy after the first. Data suggest a 40% decrease in the risk for epithelial ovarian cancer with the first live birth.[15,17] These data support theories that suggest that the hormonal changes associated with pregnancy provide a respite from continuous ovarian exposure to estrogen, a known mitogen.[15]

Smoking

While cigarette smoking as a causative factor for other gynecologic cancers is well documented,[1–2] the relationship between smoking and ovarian cancer is not as clear. However, metabolites of nicotine, including cotinine and benzo[a]pyrene-DNA (B[a]P-DNA) adducts, have been found in ovarian follicular cells.[51] In addition, polycyclic hydrocarbons such as dimethylbenzanthracene are known to induce ovarian cancer in rodents.[56] The theoretical mechanisms that may explain how cigarette smoke impacts malignant ovarian transformation include altering steroid metabolism and concentration and impairing ovarian function.[49] Seven studies have examined the relationship between smoking and ovarian cancer risk. [49, 52–57] Five of these studies were conducted outside of the US and found a statistically significant relationship between smoking and increased risk for ovarian cancer.[49,51,55–57] However, two studies conducted in the US failed to confirm this finding.[53–54]

Talc Use/Asbestos Exposure

Talcum powder (talc) use was implicated in ovarian cancer risk in the early 1960s when it was found to be biologically similar to asbestos, a known carcinogen.[58] Women exposed to asbestos in their reproductive years have a two-fold increased risk for ovarian and other cancers of the pelvis in a dose dependent manner.[61] Several studies found a positive association between talc use and increased risk of ovarian cancer.[59–62] These studies evaluated perineal application; use of talc in sanitary napkins/pads; as well as first application at birth; at puberty; or in adulthood; and exposure to asbestos. A meta-analysis of 16 studies that included 11,933 patients examined the effect of talc use and increased risk of ovarian cancer.[59] The use of talc conferred a 33% increased risk for ovarian cancer (RR= 1.33, 95% CI= 1.16–1.45). Two mechanisms are responsible for the increased risk for ovarian cancer in peritoneal talc users. The first mechanism is that the talc particles become entrapped in the ovarian surface epithelial (OSE) causing physiologic responses similar to “incessant ovulation”.[60] The second mechanism postulates that the presence of talc during ovulation allows it to be absorbed into the pelvic cavity where it is found in inclusion cysts. The foreign body in the inclusion cyst

ultimately forms a granuloma and initiates an acute inflammatory response.[61] It is this inflammatory response that is thought to lead to DNA damage, beginning the cascade of events necessary for tumorigenesis.[61]

GENETIC RISK FACTORS FOR OVARIAN CANCER

As mentioned previously, the two most common hereditary cancer syndromes associated with ovarian cancer include Hereditary Breast/Ovarian Cancer and Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome).[23,24] These patients are considered high-risk for ovarian cancer and the distinction between the hereditary types is based on which genetic mutation is involved in tumor development.

Hereditary Breast and Ovarian Cancer

Women who carry disease specific alleles for BRCA1 and BRCA2 are at significantly higher risk of epithelial ovarian cancer than women in the general population.[1–2, 23–24] The BRCA1 gene is an oncosuppressor gene located on chromosome 17q that was identified in 1994.[13] It contains small deletions or insertions that result in premature stop codons that shorten (truncate) its protein product.[15] Alterations in this gene are found in 75% of families with HBOC. The BRCA 1 gene participates in chromatin remodeling processes, interacts with the retinoblastoma (Rb) gene, and is a key member of the histone deacetylase complex. This gene participates in crucial steps within the cell cycle. When mutations occur, cellular growth controls are unchecked, which results in tumorigenesis.

The BRCA2 gene, located on chromosome 13q is found in 10% to 20% of HBOC and was isolated a year after the BRCA1 gene.[13, 15, 23–24] The BRCA1 and BRCA2 gene share sequence homology, although relatively speaking the BRCA2 gene is associated with a higher risk for breast than ovarian cancer compared to BRCA1. BRCA 2 is also associated with male breast cancer, as well as prostate and pancreatic cancer.

While no standard clinical definition of HBOC exists several general characteristics are used to identify affected families. These familial characteristics include: 1) several cases of breast cancer diagnosed before the age of 50; 2) one or more relatives with ovarian cancer; 3) one or more relatives with both breast and ovarian cancer; and 4) the presence of a BRCA1 or BRCA2 germline mutation. Ovarian cancers associated with BRCA1/2 are typically high grade serous carcinomas, but with a relatively favorable clinical course.

HNPCC/Lynch Syndrome

HNPCC/Lynch Syndrome is an autosomal, dominant syndrome, where the mean age of onset of colorectal cancer is 45 years old.[15] Famlies that exhibit HNPCC/Lynch includes, colorectal cancer and increased risk of endometrial, ovarian, gastric, pancreatic, and biliary tract cancers.[15, 23–24] Unlike HBOC, HNPCC has a standardized clinical definition, termed the Amsterdam II criteria. These criteria include: 1) 3 or more relatives with colorectal or other Lynch associated cancer, one of whom is a first degree relative to one of the other two; 2) affected members in at least 2 generations; 3) at least one Lynch associated diagnosis in the family prior to age 50; and 4) exclusion of a diagnosis of familial adenomatous polyposis.

HNPCC/Lynch Syndrome is a result of mutations in mismatch repair (MMR) genes that are found on at least four chromosomes (2p, 3p, 7p,2q). These genes form heterodimers, which recognize and repair deoxyribonucleic acid (DNA) mistakes during transcription. Mutations in MMR genes are associated with a 9% to 12% increase in the risk for ovarian cancer. Unlike the BRCA1/2 associated tumors, ovarian tumors that develop from this genetic mutation represent all histopathologic types.[15, 23] Autosomal dominant mutations such as HNPCC have a 50% chance of being transferred to offspring of the affected parent.[13] Additionally, these

mutations are highly penetrant, meaning there is a high probability of developing one of the tumors associated with HNPCC at some point during the offspring's lifetime.

NURSING IMPLICATIONS

Nurses can use the information provided in each section of this paper to improve care for cancer patients in at least three distinct ways. Nurses can integrate this information in patient teaching and clinical care. During routine physical examinations (where the majority of stage I and stage 2 ovarian tumors are detected), nurses can assess family histories and construct thorough family pedigrees. Pedigrees are a graphical representation of a family tree or history using standardized symbols that nurses can use to screen for families with potential hereditary syndromes.[13] Data obtained from the pedigree can be used to refer patients for risk assessment and genetic counseling.

Second, nurses who conduct research with healthy women can include key variables in their studies that can contribute to our understanding of the demographic and epidemiologic factors that impact the risk of healthy women developing ovarian cancer. Nurses collect data from women and their families that may contribute to refining the risk factors for ovarian cancer and possibly identifying high-risk subgroups susceptible to these tumors. Additionally, nurses can use the Ovarian Cancer Symptom Index in research studies to determine its sensitivity and specificity in low-risk, healthy women.

Finally, nurses can disseminate this information to their co-workers, family members, and other women in their lives to increase awareness of the potential risk factors for ovarian cancer.

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