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# Epidemiology and Etiology of Ovarian Cancer

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## 1. Introduction

Ovarian cancer is the second most common gynecological malignancy following uterine corpus cancer and it is the fifth leading cause of cancer death in women.

There are important differences in their incidence across the world. In Europe in 2008, estimated incidence was 66,734 cases with an estimated mortality of 41,929 women.

In United States, ovarian cancer was diagnosed in 21,880 with 13,850 cancer deaths last year. Both incidence and mortality are declining in USA and Europe.

Higher incidence rates are observed in North America and European countries exceeding 10 per 100.000 inhabitants. Lower rates are observed in South America (7,7 per 100.000) and Southern Asia (7,5 per 100.000). (Parkin et al, 2005)

Such geographical variations are due to differences in oral contraceptive use practices, pregnancy history, breast-feeding and other hormonal factors. (Permuth -Wey & Sellers, 2009)

The relative risk for developing ovarian cancer is 1.39% (lifetime risk). It affects 12.9 per 100,000 women per year. Incidence rate of ovarian cancer increases with aging, being more prevalent in the eighth decade of life.

At diagnosis, mean age is 63 years, and 62% of patients have advanced disease. Inherited ovarian cancer presents at younger age. (www.Seer.gov, Ferlay et al 2010)

Five year overall survival is 93.5% for localized disease, 73.4% for locoregional disease (regional lymph node involvement) and 27.6% for distant disease.

Genetic studies on ovarian cancer indicate that most of the cases are sporadic while 5 to 10 percent are inherited, generally due to germline mutations.

Three histological subgroups have been described: epithelial tumours, stromal tumours and germ-cell tumours. Ninety percent of cases are epithelial tumours arising from the ovarian surface epithelium or Mullerian derivatives. These tumours are typical in postmenopausal women. The World Health Organization classification defines six more histotypes: serous, mucinous, endometrioid, clear cell and squamous cell carcinomas.

According to their architectural features like glandular or papillary components, carcinomas have been classified into three histological grades, well differentiated, moderately differentiated, poorly or undifferentiated.

Malignant germ cell tumour affects younger women. (De Vita et al, 2009)

Despite the high incidence, ovarian cancer etiology is still poorly understood.

The learning objective of this chapter is to review some hormonal, environmental, inherited risk and protective factors associated with ovarian cancer.

## 2. Risk and protective factors

### 2.1 Reproductive and hormonal factors

Hormones such as estrogen and progesterone are believed to be involved in promoting ovarian carcinogenesis. Several hypotheses have been postulated.

The “incessant ovulation theory” holds that the risk of ovarian cancer is increased through the repetitive ovulatory microtrauma to the ovarian epithelium. The number of ovulatory cycles increases the rate of cellular division associated with the repair of the surface epithelium after each ovulation, thereby increasing the likelihood of spontaneous mutations that might promote carcinogenesis.

Breast-feeding, pregnancy or oral contraceptive that suppress ovulation would have a protective effect. (Casagrande et al,1979).

The “pituitary gonadotropin hypothesis” indicates that high levels of estrogens and gonadotropins such as luteinizing hormone and follicle-stimulating hormone would over stimulate ovarian epithelium causing increased proliferation and subsequent malignant transformation (Cramer et al,1983).

Another hypothesis has described that androgens may stimulate ovarian cancer formation whereas progestin are protective. (Risch et al,1998)

The “inflammation hypothesis” proposes that factors such as endometriosis, pelvic inflammatory disease and other inflammatory conditions may stimulate cancer formation. (Ness et al,2000)

The last hypothesis, also called “the ovarian stromal hypothesis” states that there may be a failure of the apoptosis of the granulosa and theca cells after ovulation which continued producing steroid hormones, thereby stimulating the formation of cancer. (Vo et al,2007; Purdie et al,2003;Permuth-Wey & Sellers,2009)

#### 2.1.1 Early menarche and late menopause

Due to support the incessant ovulation hypothesis early age at menarche (less than 12 years) and late age at menopause (more than 50 years) should increase the number of ovulatory cycles. Several epidemiological studies have examined this relationship showing a slight increase among women with early age at menarche, Odds Ratio (OR) ranging from 1,1-1,5 and women with late age at menopause with OR ranking from 1,4-4,6 (Permuth-Wey& Sellers,2009).

In contrast to these data another prospective study in healthy nurses found no association between age at menarche and menopause and ovarian cancer risk. (Hankinson et al,1995)

#### 2.1.2 Pregnancy

Nulliparous women tend to have more ovulatory cycles than multiparous women. It has been shown that with each full ovulation year there is a 6 percent increase in risk of ovarian cancer. This finding is specially relevant in the 20 to 29 year age group in which the risk is highest with a 20 percent increase.(Purdie et al,2003) Pregnancy also causes anovulation and suppresses secretion of pituitary gonadotropins. Maternal age of last birth is also implicated in decreasing the risk of ovarian cancer if the last birth was at age of 35 or greater.

Several case-control studies have demonstrated that parous women are estimated to have a 30-60% lower risk for ovarian cancer. Increasing parity seems to reduce risk further. In a recent case-control study between parous and non parous women, higher parity, increased age at first or last birth, and time since last birth were associated with reduced risk of ovarian cancer. This was due to endometrioid and clear cell histology. This link was correlated with reduced risk of epithelial ovarian cancer in another studies. (Titus-Ernstoff et al,2001;Hinkula et al,2006;Whiteman et al,2000) In another prospective study which examined several hormonal factor in 121.700 healthy nurses between 35 to 55 years a statistically significant inverse association was observed between parity and ovarian cancer risk (relative risk [RR] = 0.84; 95% confidence interval [CI] = 0.77-0.91 per pregnancy) ; age at first birth was not associated independently with risk (Hankinson et al,1995). A history of incomplete pregnancy does not influence a woman's risk of epithelial ovarian cancer (Dick et al,2009). Age at last birth also has been strongly associated with a reduced risk of ovarian cancer. Women with a last birth after age 30 to 35 years have a 58% decreased risk for ovarian cancer compared with nulliparous women. One theory to explain this also called the exfoliate theory is based on the suspicion that older women are more likely than younger women to have accumulated transformed surface epithelial ovarian cells, and progestins as suggested before may induced apoptosis of this cells, reducing the account of cells susceptible of malignant transformation (Whiteman et al,2003).

### **2.1.3 Breastfeeding**

Breastfeeding suppresses the secretion of pituitary gonadotropins leading to anovulation. Several studies have demonstrated an inverse association between ovarian cancer and lactation especially for non mucinous subtypes. An increasing period of breastfeeding has also been reported to decrease ovarian cancer risk. (Negri et al,2005;Chiafafrino et al,2005;Chiaffarino et al,2007;Jordan et al,2010) Danforth et al demonstrated that breastfeeding 18 or more months was associated with a significant decrease in ovarian cancer risk compared to never breastfeeding (RR=0.66, 95% CI 0.46-0.96). For each month of breastfeeding the relative risk decreased by 2 percent (RR=0.98 per month, 95% CI 0.97-1.00). (Danforth et al,2007)

### **2.1.4 Endometriosis**

Endometriosis and its hormonally regulated lesions may trigger a local inflammatory reaction with activation of macrophages releasing cytokines and growth factors. Some clinical series have identified the coexistence of endometriosis and ovarian cancer particularly clear cell histology. (Ness et al,2000;Orezzoli et al,2008)

A Canadian cohort study also confirmed this association. They found an anticipation of 5, 5 years between people with endometriosis and ovarian cancer and also an increased risk of ovarian cancer. (Ariset al,2010)

### **2.1.5 Pelvic inflammatory disease and polycystic ovarian syndrome**

Pelvic inflammatory disease has been linked to an increased risk of ovarian cancer, and more if it occurred at an early age, if the women were nulliparous, infertile or had experienced recurrent episodes.(Risch,1995)

Common clinical presentations of polycystic ovarian syndrome (PCOS) include obesity, hirsutism, infertility and menstrual abnormalities. Women with PCOS has an elevated

luteinizing hormone to follicle stimulating hormone ratio, hyperandrogenism and abnormal estrogens secretion. Ovarian cancer risk seems higher among women who does not use oral contraceptives. However these data are controversial. Balen et al,2001)

### 2.1.6 Hormone replacement

The use of hormonal agents such as infertility treatment and their association with ovarian cancer has been subject of discussion for years. The Women's Health Initiative (WHI) study found an increased risk for ovarian cancer with a hazard ratio of 1,58.(Anderson et al,2003)

A metaanalysis of eight cohort and 19 case-control studies found a summary relative risk (RR) of 1.24 (95% confidence interval [CI] 1.15-1.34) from cohort studies and a summary odds ratio [OR] of 1.19 (95%CI 1.02-1.40) from case-control studies for ever Hormone replacement therapy (HRT) use. Association was stronger among ERT (estrogen replacement treatment) user than EPRT (estrogen-progestin replacement treatment) user. Based on data abstracted from six case-control studies, duration of HRT use was not significant. The summary risk estimates for less than 5 years, 6-10, and more than 10 years use were 1.02, 1.13, and 1.21, respectively and 95%CI for each estimate crossed 1.0.(Zhou et al,2008) Another observational study from UK in postmenopausal women with no risk factor for ovarian cancer reported that current users of HRT were significantly more likely to develop and die from ovarian cancer than never users (relative risk 1.20 [95% CI 1.09-1.32; p=0.0002] for incident disease and 1.23 [1.09-1.38; p=0.0006] for death). Ovarian cancer increased with increasing duration of use, but did not differ significantly by type of preparation used, its constituents, or mode of administration. Serous carcinoma was more common associated than mucinous, endometrioid, or clear cell tumours. Past users of HRT were not at an increased risk of ovarian cancer. (Beral t al,2007)

The time association between the duration of use of HRT and the risk of development ovarian cancer seems to be between 5 and 10 years and may last up to 29 years after HRT use has stopped. (Danforth et al,2007) In contrast to these findings a recent Danish study found no overall increased risk of ovarian cancer was showed after any use of gonadotrophins, clomifene , human chorionic gonadotrophin , or gonadotrophin releasing hormone. Furthermore, no associations were found between all four groups of fertility drugs and number of cycles of use, length of follow-up, or parity.(Jense et al,2009)

### 2.1.7 Oral contraception

Several studies have demonstrated that oral contraception decreases the risk of ovarian cancer due to reduction in ovulatory cycles.

Women using oral contraceptives had a risk reduction of ovarian cancer of at least 30 to 40 percent with Lower risk with longer time of use. Use oral contraceptive for more than five years was found to have a stronger reduction than use for less than five years.

In a large review of twelve case-controlled studies in the United States , use of oral contraceptives and reduction ovarian cancer risk had an overall odds ratio of 0,67(95%CI 0,37-1,2) in white women.(Whittemore et al, 1992).

This protective effect continued 15 to 20 years after ceased and was independent of any specific type of oral contraceptive formulation. (Bosetti et al,2002;La Vecchia et al,2006).

In another reanalysis of data of 45 epidemiological studies use of oral contraceptives confers long-term protection against ovarian cancer suggesting that oral contraceptives have

already prevented some 200,000 ovarian cancers and 100,000 ovarian cancer related deaths.(Beral et al,2008)

This was also reported in both carriers and non-carriers of BRCA1 mutation. Reduced risk of ovarian cancer was associated with the use of oral contraceptives, odds ratio of 0.54 (95% confidence interval (CI): 0.26, 1.13) for carriers and 0.55 (95% CI: 0.41, 0.73) for non-carriers. Tubal ligation and increasing parity were also associated with reduced risk. (McGuire et al,2004)

Use for more than five years confers a protective factor for up to 10 years after discontinuation.

### **2.1.8 Tubal ligation and hysterectomy**

Tubal ligation has been documented to decrease the risk of development epithelial ovarian cancer, especially endometrioid tumours. This has been postulated as a result of the reducing utero-ovarian flow and altering local hormonal and growth factor levels. This was also demonstrated for hysterectomy. (Parazzini et al,1993;Tung et al,2003)

## **3. Environmental factors**

Obesity and increasing body mass index (BMI) have been associated with ovarian cancer risk. In a combined study of cohorts BMI was not associated with ovarian cancer risk in postmenopausal women but was positively associated with risk in premenopausal women (Schoute et al,2008). A meta-analysis also concluded that being obese (defined as a body mass index over 30) or overweight in the premenopausal years is associated with an increased risk of ovarian cancer, suggesting a possible influence of menopausal status on the endogenous hormonal environment.(Olsen et al,2007)

The risk of ovarian cancer may result from changes in synthesis and bioavailability of endogenous sex esters seen in obese women. (Vo et al,2007)

Exposure to talc was associated with ovarian cancer risk due to perineal migration in the past. Nonetheless a meta-analysis did not find any association.(Harlow et al,1992;Huncharek et al,2007)

Cigarette smoking increases risk of mucinous and borderline ovarian tumours but not other histological subtypes. (Zhang et al,2004;Rossing et al,2008).

Hankinson et al studied the relationship between ovarian cancer and several environmental factors. They found in a prospective study which examined 110,454 women that compared with never-smokers, neither current nor past smoking was associated with ovarian cancer risk overall; however, both situations were associated with mucinous tumors (n = 69; rate ratio [RR], past = 2.02 [95% confidence interval (CI), 1.15-3.55]; RR, current = 2.22 [95% CI, 1.16-4.24]). A modest inverse association between caffeine intake and ovarian cancer risk was observed (RR, top vs bottom quintile = 0.80; 95% CI, 0.60-1.07 [P = .03]), which was strongest for women who had never used either oral contraceptives (RR = 0.65; 95% CI, 0.46-0.92 [P for heterogeneity = .02]) or postmenopausal hormones (RR = 0.57; 95% CI, 0.36-0.91 [P for heterogeneity = .13]). Alcohol was not associated with ovarian cancer risk (Hankinson et al,2008).

Another data from alcohol and caffeine intake and ovarian cancer risk are inconclusive.

The impact of diet and physical activity is unknown.

La Vecchia et al found in a case- control study between italian women that meat consumption over 7 portions versus less than 4 portions of meat per week (RR:1,6;95%CI:1,21-2,12)

increased ovarian cancer risk and also the consumption of butter versus fat consumption (RR:1,9;95% CI:1,20-3,11). However some confounding factors were present in the study like body weight, parity, socioeconomic status and contraceptive use. The Women's Health Initiative Dietary Modification Randomized Controlled Trial demonstrated decreased ovarian cancer risk in postmenopausal women after four years of a low-fat diet, although this was not statistically significant. Increased daily fiber intake; the use of carotene, vitamin C, vitamin E, and unsaturated fatty acids; and increased physical activity were moderately associated with a decreased risk of ovarian cancer. However, several confounding factors may coexist, and there is limited evidence to support recommending specific lifestyle modifications to reduce ovarian cancer risk. (Prentice et al,2007)

Another prospective study did not find some relation between consumption of antioxidant vitamins from foods or supplements, or intake of fruits and vegetables, and the incidence of ovarian carcinoma (Fairfield et al,2001).

Milk, calcium and lactose intake were associated with reduced risk in another case-control study. The odds ratio for ovarian cancer was 0.46 (95% confidence interval: 0.27, 0.76) among women in the highest quartile of dietary calcium intake versus the lowest (p for trend = 0.0006). The significant dietary association was limited to dairy sources of calcium (p for trend = 0.003), although a nonsignificant inverse gradient in risk was also found in relation to calcium supplement intake (Goodman et al,2002).

Non steroidal anti-inflammatory drugs have been described as a protective factor of ovarian cancer.

Several hypotheses have been postulated like interruption prostaglandin synthesis, apoptosis induction and reduction local inflammatory processes.

Two case-control studies have found a relationship between acetaminophen use and reduction in ovarian cancer risk. (Rosenberg et al, 2000; Cramer et al,1998)

Despite this, the influence of environmental factors in the etiology of ovarian cancer is controversial.

#### **4. Genetic factors**

One of the most significant risk factors of ovarian cancer is a familial history of the disease. Mutations in genes involved in DNA repair (BRCA, MSH-2, MLH-1, PMS 1 and 2) increases risk of cancer in some individuals.

It is estimated that approximately 7 percent of women with ovarian cancer have a positive family history of the disease. (Nguyen et al, 1994)

Genetic factors account for 10 to 15 percent of ovarian cancer cases.

Population-based studies have identified a personal history of breast cancer (particularly at young age) or a family history of either breast or ovarian cancer as one of the strongest risk factors, increasing woman's risk two to six fold. Hereditary ovarian cancer generally occurs in women about 10 years earlier than sporadic disease (Negri et al,2003;Nguyen et al,1994; Parazzini et al 1992; Stratton et al 1998;Sutcliffe et al 2000; Ziogas et al 2000).

We should differentiate genetic factors into two different subtypes as are familiar ovarian cancer and hereditary ovarian cancer.

##### **4.1 Familiar aggregation**

Women with a single family member affected by epithelial ovarian cancer have a 4 to 5 percent risk, while those with two affected relatives have a 7 percent risk for developing the

disease in absolute numbers (Carlson et al,1994). In relative numbers familiar ovarian cancer confers a 4,6 percent relative risk (95% CI =2,1-8,7) of this disease in the proband's mother and 1,66 relative risk (95% CI=0,2-5,9) in the proband's sister.(Ziogas et al,2000)

#### 4.2 Hereditary factors

At least 10 percent of ovarian tumours are hereditary and associated with highly penetrant, autosomal dominant genetic predisposition.

The two most common hereditary cancer syndromes associated with ovarian cancer include Hereditary Breast Ovarian Cancer that accounts for approximately 90 percent of the cases and Ovarian Cancer and Hereditary Nonpoliposis Colorectal Cancer (Lynch Syndrome) that accounts for the 10 percent of the cases.(Russo et al,2009)

Hereditary ovarian cancer syndromes appears to be genotypically and phenotypically an heterogeneous disease characterized by variable clinical courses.

##### 4.2.1 Hereditary Breast - Ovarian Cancer (HBOC) syndrome

Women who carry disease specific alleles for BRCA1 and BRCA2 are at significantly higher risk of epithelial ovarian cancer than general population. The BRCA1 is an oncosuppressor gene located on chromosome 17q21. It was first identified in 1994 and contains small deletions or insertions that result in premature stop codons that shorten (truncate) its protein product. This gene participates in chromatin remodelling processes and when mutation occurs cellular controls are unchecked resulting in cellular overgrowing. Alterations in this gene are found in 75 percent of families with hereditary breast and ovarian cancer. On the other hand BRCA2 is a suppressor gene located on chromosome 13q. Its alterations are found in 10 to 20 percent of families with hereditary breast and ovarian cancer.

More than 2600 mutations have been found in those chromosomes. They have been described in 1/800 people in the general (White) and 1/40-50 in ashkenazi Jewish. Mutations in these genes lead to inability to regulate cell death and uncontrolled cell growth leading to cancer. (Carroll et al,2008)

The average cumulative risks in BRCA1-mutation carriers by age 70 years were 39 percent (18%-54%) for ovarian cancer. The corresponding estimates for BRCA2 were 11 percent (2.4%-19%). (Antoniou et al,2003)

Type of Cancer	BRCA Mutation Carriers (%)	General Population (%)
Breast (women)	50-85	11
Breast (men)	≤6	Rare
Ovarian (BRCA1)	40-60	1,5
Ovarian (BRCA2)	10-20	1,5

Table 1. Estimated risk of developing cancer by age 70 in BRCA mutation carriers with the general population.



In contrast to Lynch syndrome there are no defined criteria for this hereditary syndrome. Some criteria have been described and these include several cases of breast cancer diagnosed before the age of 50, one or more relatives with both breast and ovarian cancer, the presence of BRCA1 or BRCA 2 germline mutation. These criteria vary between the different Cooperative Groups.

<p><b>Independent of Family History</b></p> <ul style="list-style-type: none"> <li>• Patient with synchronous or metachronous breast and ovarian cancer</li> <li>• Breast cancer before 30 years</li> <li>• Bilateral breast cancer before 40 years</li> </ul>
<p><b>Families with two affected breast or ovarian cancer an one of the next characteristics:</b></p> <ul style="list-style-type: none"> <li>• Male breast cancer</li> <li>• Ovarian, primary peritoneal or Fallopian tube cancer</li> <li>• Both two cases before 50 years</li> <li>• One bilateral case and the other before 50 years</li> </ul>
<p><b>Families with 3 or more affected members with breast or ovarian cancer</b></p>

Table 2. Criteria for Mutation in BRCA1-BRCA 2 genes study.

Special mention deserves triple negative breast cancer associated with familiar history of breast or ovarian cancer and younger age at diagnosis. It confers a special risk for BRCA1 mutation although criteria have not yet been defined (Young et al, 2009;Haffty et al, 2006)

Some statistical models have been investigated to estimate the risk of having a germline mutation in BRCA1 and BRCA 2 genes like Boadicea, BRCA PRO, Manchester, IBIS, Myriad II, U Penn.

Ovarian cancers associated with BRCA1-2 mutation are typically high grade serous bilateral carcinomas.

There exist some controversies about the prognosis of these neoplasms. The information derives from retrospective studies, with intrinsic bias due to inadequate sample size and also the lack of adequate controls.

Some case-control and population studies found no difference in survival between general population and mutations carriers (Brunet et al,1997;Johannsson et al,1998) Another studies show a more favourable outcome in mutation carriers.(Rubin et al,1996)

Tan et al. described in a small case-control study that BRCA-positive patients had higher overall (95.5% v 59.1%;  $P = .002$ ) and complete response rates (81.8% v 43.2%;  $P = .004$ ) to first line chemotherapy treatment, higher responses to second and third line platinum-based chemotherapy (second line, 91.7% v 40.9% [ $P = .004$ ]; third line, 100% v 14.3% [ $P = .005$ ]) and longer progression free interval. A significant improvement in median OS in BRCA-positive patients compared with controls was observed from both time of diagnosis (8.4 v 2.9 years;  $P < .002$ ) and time of first relapse (5 v 1.6 years;  $P < .001$ ). BRCA status, stage, and length of first response were independent prognostic factors from time of first relapse. (Tan et al,2008)

Some preventive strategies like bilateral salpingo-oophorectomy or mastectomy have been developed to prevent these neoplasms.

Salpingo-oophorectomy has demonstrated a risk reduction of ovarian cancer over 90 percent and a 50 percent for breast cancer with a mean follow up time of 5 years. (Agnantis et al,2004;Dowdy et al,2004)

Rebbeck et al report that bilateral salpingo-oophorectomy was associated with a statistically significant risk reduction of BRCA1/2-associated ovarian or fallopian tube cancer (HR = 0.21; 95% CI = 0.12 to 0.39), which confers an absolute risk reduction near 80 percent of ovarian and fallopian tube neoplasm.(Rebbeck et al,2009)

Another neoplasm has been associated with these mutations. In BRCA 1 carriers primary peritoneal cancer, fallopian tube cancer and prostate cancer have been described. In BRAC 2 carriers there are also an increased risk for melanoma, pancreatic cancer, gastric cancer and biliary tract cancer. (Llort et al,2010)

#### 4.2.2 Hereditary nonpolyposis colorectal cancer (lynch syndrome)

Lynch and co-workers described in 1966 a syndrome that conferred a susceptibility to colorectal cancer with predilection to the right of the splenic flexure but with no excess of adenomatous polyps in younger than expected in adult patients (<45 years) (Lynch et al,1967)

This is an autosomal dominant syndrome which increases risk of colorectal endometrial, ovarian, gastric, pancreatic , renal and biliary tract cancer and it is a result of mutations in mismatch repair (MMR) genes including at least four chromosomes (2p,3p,7p,2q).These genes form heterodimers which recognize and repair deoxyribonucleic acid mistakes during transcription.

Watson et al determined a 6,7 percent lifetime risk for ovarian cancer in proven or probable MSH2 and MSH1 mutation carriers (Watson et al,2008).

Some clinical criteria have been described to identify Lynch syndrome.

Amsterdam criteria were first described in 1990 called Amsterdam I. They were revised in 1999 (Vasen et al, 1999).

<b>Amsterdam I</b>
<ol style="list-style-type: none"> <li>1. At least 3 relatives with histologically confirmed colorectal cancer, 1 of whom is a first degree relative of the other 2</li> <li>2. At least 2 successive generations involved.</li> <li>3. At least 1 of the cancers diagnosed before age 50.</li> <li>4. Familial adenomatous polyposis should be excluded.</li> </ol>
<b>Amsterdam II</b>
<ol style="list-style-type: none"> <li>1. 3 or more relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis);</li> <li>2. 2 or more successive generations affected;</li> <li>3. 1 or more relatives diagnosed before the age of 50 years;</li> <li>4. 1 should be a first-degree relative of the other two;</li> <li>5. Familial adenomatous polyposis (FAP) should be excluded in cases of colorectal carcinoma;</li> <li>6. Tumours should be verified by pathologic examination</li> </ol>

Table 3. Amsterdam I and II.

Then in 1996 Bethesda criteria were redacted to encompass a greater number of patients who may be carriers of a mutation.

They have found to be more sensitive than Amsterdam criteria.

Bethesda Criteria:

1. Individuals with cancer in families meeting the Amsterdam criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers an individual and a first-degree relative with:
  - either colorectal cancer
  - and/or HNPCC-related extracolonic cancer
  - and/or a colorectal adenoma
  - One of the cancers diagnosed at age <45 years, and the adenoma diagnosed at age <40 years
3. Individuals with colorectal cancer or endometrial cancer diagnosed at age <45 years.
4. Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribiform) on histopathology diagnosed at age <45 years
5. Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45 years.
6. Individuals with adenomas diagnosed at age <40 years

Revised Bethesda criteria:

1. CRC diagnosed in individual under age 50 years.
2. Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, regardless of age.
3. CRC with the MSI-H histology (presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern), in patient 60 years of age.
4. CRC in 1 or more first-degree relatives with an HNPCC-related tumor, with 1 of the cancers being diagnosed under age 50 years.
5. CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC- related tumors, regardless of age.

(Rodriguez-Bigas et al,1997;Umar et al,2004)

Ovarian cancer from this syndrome at diagnosis is ten years earlier than in general population and survival is similar as sporadic ovarian cancer. It represents all histopathologic subtypes.(Crijnen et al,2005)

There are no proven strategies that have demonstrated an impact on survival in this setting.

<b>Increased Risk</b>	<b>Decreased Risk</b>
Delayed childbearing	Breastfeeding for 18 months or more
Early menarche	Early menopause
Endometriosis	Multiparity (risk decreases with each additional pregnancy)
Estrogen replacement therapy for more than five years	Hysterctomy
Family History suggesting genetic predisposition	Late menarche
Genetic syndromes	Low fat diet
Hight fat diet	Tubal Ligation
Late menopause	
Low parity	

Table 4. Risk Factors Associated with Ovarian Cancer.

## 5. Conclusion

Ovarian cancer is the second most common gynecological malignancy and the fifth leading cause of cancer death. Some histological subgroups have been described. Etiology is still poorly understood. Hypotheses relating to incessant ovulation, excessive gonadotropin secretion have been involved as etiological explanations. Based upon epidemiological research there is evidence that certain reproductive factors are associated with ovarian cancer risk. There are some hormonal factors that have special importance. Each childbirth incurs a 15 to 20 percent reduction risk. Breastfeeding also represents a protective factor. Oral contraceptive use for 5 years or longer reduced about half the risk compared to never users. In contrast to these protective factors hormone replacement therapy compared with never users increases the risk and this is associated with longer use. Some inflammatory disorders like pelvic inflammatory disease and endometriosis are associated with an increased risk. The significance of environmental factors like obesity, cigarette smoking, vegetable consumption etc is not yet established. Finally some genetic disorders like BRCA 1 and 2 mutations and Lynch syndrome have been involved as risk factors for this disease. A deeper understanding of these risk factors is important in order to establish preventive strategies for this fatal disease

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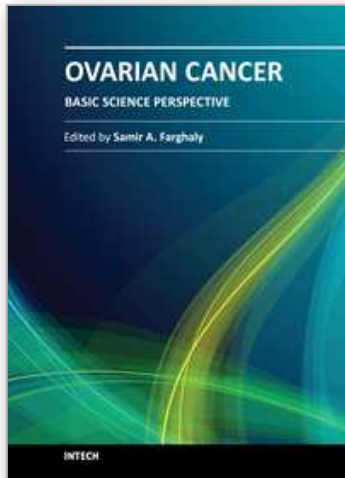
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Worldwide, Ovarian carcinoma continues to be responsible for more deaths than all other gynecologic malignancies combined. International leaders in the field address the critical biologic and basic science issues relevant to the disease. The book details the molecular biological aspects of ovarian cancer. It provides molecular biology techniques of understanding this cancer. The techniques are designed to determine tumor genetics, expression, and protein function, and to elucidate the genetic mechanisms by which gene and immunotherapies may be perfected. It provides an analysis of current research into aspects of malignant transformation, growth control, and metastasis. A comprehensive spectrum of topics is covered providing up to date information on scientific discoveries and management considerations.

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