Current Treatment Options in Oncology (2009) 10:67–81
DOI 10.1007/s11864-009-0108-2

Gynecologic Tumors

Current Understanding of Risk Factors for Ovarian Cancer

Thanasak Sueblinvong, MD
*Michael E. Carney, MD**

Address
**Department of Obstetrics and Gynecology, John A Burn School of Medicine, 1319 Punahou St. suite #640, Honolulu, HI 96826, USA,*
E-mail: mcarney@hawaii.edu

Opinion statement

Ovarian cancer is the deadliest gynecologic cancer. Unlike many cancers such as breast, cervical and colon cancers, there is no easily clinically identifiable pre-malignant phase of this malignancy making early identification difficult. Similarly, unlike lung, head and neck, and skin cancers, there is not easily identifiable risk factor making prevention short of oophorectomy difficult. Even so, theories as to the causative factors of ovarian cancer continue to evolve making our understanding of the genesis of ovarian cancer more clear. Genetics, parity, environment, hormonal factors, and inflammation all play an important and pivotal role in the development of ovarian cancer. The most current understanding of these elements and their respective contribution to the development of this cancer are presented in this chapter.

Introduction

The deadliest gynecologic cancer is epithelial ovarian cancer (EOC) with some 26,650 new cases in the United States yearly and some 16,000 deaths [1]. A woman's risk of getting ovarian cancer during her lifetime is relatively low at about one in 71 but most will die of their disease. Fortunately, three of four women with ovarian cancer survive at least one year after the diagnosis. Unfortunately, three of four women will die of their disease in five years. Overall, a woman's lifetime chance of dying from invasive ovarian is about one in 95.

Westernized industrialized countries, particularly in Europe, Canada, and North America, have the highest rates of this cancer [2]. Several relatively minor epidemiologic risk factors have been identified as increasing the risk of ovarian cancer including low parity, infertility, early age of menarche, and late age of menopause [3]. The pathogenesis of ovarian carcinoma, unlike many other cancers, remains unclear. Several theories have been proposed to explain the epidemiology of ovarian cancer including:

1. Incessant ovulation, whereby, with repeated damage and trauma to the ovarian epithelium during each ovulatory cycle, there is an increased potential for genetic mutation and ovarian neoplasm during the repair process [4, 5].
2. The pituitary gonadotropin hypothesis, which postulates that high levels of gonadotropins increase stimulation of estrogen, which can cause ovarian epithelial cells to become entrapped in inclusion cysts and undergo malignant change [2, 6].
3. The androgen/progesterone hypothesis, which suggests that androgens may stimulate ovarian

cancer formation, whereas progestins are protective [2, 6, 7].

4. The inflammation hypothesis, which proposes that factors that predispose to inflammation, such as endometriosis, pelvic inflammatory disease, perineal talc use, and hyperthyroidism, may stimulate ovarian cancer formation [2, 8].
5. The ovarian stromal hypothesis, which states that there may be a failure of apoptosis of granulosa and theca cells after ovulation, these cells continue to produce steroid hormones, thereby stimulating the formation of cancer [2, 9].

Associated risk factors for ovarian cancer support many of these hypotheses. For example, oral contraceptive use is consistently associated with a decreased risk of ovarian cancer and may operate through preventing the trauma from repeated ovulation as well as by lowering exposure to gonadotropins. No one theory, however, explains all the associated risk factors.

This article will review factors that increase or decrease the risk of ovarian cancer. These factors are categorized into reproductive factors, exogenous hormones, gynecology-related conditions, environmental factors, and genetic factors.

Reproductive factors

Parity and pregnancy

- A consistent finding in ovarian cancer epidemiology is the protection from EOC observed among parous compared with nulliparous women. The association was observed in both case–control and cohort studies [10–17]. The odds ratios (ORs) of EOC for parous compared to nulliparous women in several case–control studies ranged from 0.3 to 0.7 [14, 18]. Increasing parity also seems to reduce EOC risk further. Significantly reduced risks of EOC were demonstrated in a pooled analysis of 12 US-based case–control studies, with a 40% lower risk after the first birth, while each additional birth incurred another 14% risk reduction [14]. An OR for EOC of 0.32 (95% CI 0.18–0.56) was reported among women who had given birth to five or more children compared to nulliparous. Parous women also seem to be at reduced risks of borderline ovarian tumor (BOT), although the protection seems to be weaker than that seen for EOC [12, 19–23]. Histology-specific risk estimates indicate a protective effect of parity against all types of EOC and BOT [13, 19] except possibly for mucinous tumors, where positive, inverse [10, 13, 19, 20] and absent associations have been reported [23]. Several case–control studies also found a positive association between a late age at first birth and the risk of EOC [14, 17, 18]. In the Swedish study, each 5-year increment in age at first birth appeared to reduce EOC risk by 10% and the effects were stronger for EOC than BOT [12].
- A Swedish population-based cohort in 2008 also found a relationship between a high placental weight to an increased risk of developing invasive EOC at a young age [24]. This is consistent with a prior study from the same institution that reported that a low birth weight baby adjusted for gestational age is associated with a reduced risk of developing EOC at an early age (the mean age at diagnosis was 43 years) [25].
- For miscarriage or abortion, most studies found a slightly reduced risk [13, 14, 17] or no association with EOC [10, 15, 16]. In general, incomplete pregnancies seem to confer some protection from EOC, although the protection is weaker than that from full-term pregnancies. Incomplete pregnancies also seem to reduce the risk of BOT in some [19, 22] but not all investigations [20].
- The biological mechanism explaining the protective effect of pregnancy has not been identified. Pregnancy leads to anovulation, thereby reducing gonadotropin secretion and increasing endogenous

estrogen and progesterone levels. Furthermore, pregnancy temporarily interrupts the retrograde transportation of exogenous substances or menstrual blood through the Fallopian tubes, and presumably provides time for apoptosis. Progesterone has also been suggested to have a protective role in ovarian cancer development by suppressing epithelial proliferation, promoting cellular differentiation and apoptosis, thus removing premalignant cells from ovaries [26]. Experimental studies in animals and human cell lines have shown that administration of progestins up-regulates expression of the p53 tumor suppressor gene and induces apoptosis [27]. These data suggest that apoptosis resulting from high progesterone levels during pregnancy or from exogenous hormone could clear transformed cells in the ovarian epithelium. The postulated protective role of progesterone, however, may be outweighed by the influence of other hormonal factors during pregnancy. One concern is exposure to IGF-I which is strongly associated with risk of premenopausal ovarian cancer [28]. IGF-I, made in the placenta, increases with placental weight and rises significantly in late pregnancy [24].

Lactation

- It is well known that breastfeeding lowers a woman's risk of breast cancer. Similarly, most studies indicate that breastfeeding slightly lowers the risk of EOC. Risk estimates between 0.6 and 0.9 have been observed for parous women who have breastfed their children compared with those who never breastfed [14, 15, 24]. According to some studies, lactation during the initial months after delivery conferred stronger protection from EOC than lactation at later time periods [14]. Data from two prospective cohorts, with up to 391 EOC cases among 149,693 parous women, revealed a risk reduction, although nonsignificant, in ever breastfeeding compared to never breast feeding with a median duration of breastfeeding of 9 months (RR = 0.86, 95%CI 0.70–1.06) [29]. However, breastfeeding of 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% (RR = 0.98, 95%CI 0.97–1.00). A protective effect of lactation on EOC risk would support hypotheses linked to incessant ovulation, excess gonadotropins, retrograde transportation and apoptosis.

Age at menarche and menopause

- A large number of epidemiological studies have examined age at menarche and menopause in relation to the risk of EOC, and generally these factors appear to be weak predictors of risk. Moderately elevated risks of EOC were reported among women whose menarche occurred before 12 years of age, compared to those who were older than 14 [17, 30], although many of the ORs were not statistically significant. A population-based case–control analysis from North Carolina revealed that a young age at menarche was statistically significantly associated with a premenopausal but not a postmenopausal

risk of ovarian cancer [31]. A positive association between age at natural menopause and EOC risk appears in several case–control studies, with risk estimates across studies from 1.5 to 2.9 for the oldest menopause category compared with younger referents [17–19] supporting the incessant ovulation hypothesis but contradicting a gonadotropin hypothesis. Late age at menopause also was associated with an increased risk of BOT in some [19, 21, 22] but not other studies [20].

Exogenous hormones

Oral contraceptives

- The contraceptive effect of combined oral contraceptives (OCs), which contain both weak estrogens and more potent progestins, is mediated by suppression of the midcycle gonadotropin surge with a consequent inhibition of ovulation. Based on numerous epidemiological studies, it is now accepted that OCs protect against EOC. Ever-users of OCs compared with never-users have been at consistently lower risk of EOC in almost all case–control studies [13–17] and prospective studies [30], where this association was examined. One meta-analysis also showed a relative risk (RR) for EOC of 0.64 (95% CI 0.57–0.73) among ever-users compared with never-users of OCs [32] and similar findings were reported in other analyses [14].
- A longer duration of OC use seems to enhance the protection against EOC risk. Most studies have observed reduced risks of EOC after several years of OC use [13–17, 33, 34]; however, a risk reduction has also been found with short-term use (<1 year) in some studies [14, 34]. In a recent review, a 50% decrease in the risk of EOC was estimated after five years on the pill [35], and a similar effect was seen in a meta-analysis where each year of OC use contributed to a 10–12% risk reduction [32]. The protective effect of OCs continues for a long time after cessation of OC use. Several studies have demonstrated a 40–70% reduced risk of EOC even after 10 years had elapsed since the last use [13, 14, 17, 33, 34]. In a pooled analysis based on three European case–control studies, a 50% risk reduction still persisted after 15 years off the pill [36]. A recent population-based cohort study from North Carolina revealed an inverse association of ovarian cancer with longer duration of oral contraceptive use, later age at last use, and more recent use among premenopausal women. Contrary to overwhelming currently published data, one recent study reported no significant protective effect of contraceptive use in postmenopausal women that developed ovarian cancer [31]. Only a few studies have evaluated progestin-only contraceptives in relation to EOC risk, and although these data are sparse, a protective effect seems plausible [33, 34]. The use of OCs appears to have no effect on mucinous cancers in some studies [11, 13, 23, 34]. For BOT, OCs also appear to reduce risk when separate analysis was performed [20–23, 34].
- Suggesting a co-effect of NSAIDs and OCPs, a population-based case–control study from Wisconsin and Massachusetts found an inverse association of ever users of NSAIDs in women that never used oral contraceptives with OR = 0.58 (95%CI 0.42–0.80) but not for women that ever used oral contraceptives (OR = 0.98, 95%CI 0.71–1.35). A

reduced risk with NSAID use was also noted in nulliparous women but not among parous women [37].

Fertility medication

- Nulliparity is an established risk factor for EOC and BOT. Fertility drugs such as clomiphene citrate, human menopausal gonadotropin (hMG) and human chorionic gonadotropin (hCG) were epidemiologically linked to BOT and EOC in initial studies raising concerns about the use of these drugs and the association with elevated risk of these malignancies [38, 39]. A number of studies have addressed the central question of whether nulliparity, infertility and the use of fertility agents independently are associated with the risk of EOC and BOT. However, there were many confounding factors limiting studies among women who used infertility medications, including inconsistent definitions of infertility or subfertility, poor recall of infertility agents used by physicians and patients, the poor selection of appropriate control groups, associated endometriosis and small numbers [40].
- Infertility apart from nulliparity appeared to increase the risk of EOC in most [10, 11, 15, 17, 40, 41] but not all studies [42, 43]. Some studies observed that the increased EOC risk from infertility was restricted to women who remained childless, while temporary fertility problems among women who eventually gave birth were not related to an increased risk [14, 15, 17, 44]. A positive association between infertility and BOT also has been reported [20].
- Studies that examined infertility type in relation to EOC risk report conflicting and often statistically nonsignificant results. Elevated risks of EOC have been observed for anovulatory [45, 46], nonhormonal [47] and unexplained infertility types [41]. The most important question regarding infertility and BOT/EOC is whether the widespread use of fertility agents in assisted reproductive technology increases risk. The findings of studies where this question was addressed are conflicting. Several studies demonstrated an increased risk of EOC among those exposed to clomiphene [46], hMG [45, 46] or any ovulatory stimulants [14, 41] compared with nonexposed, whereas this was not observed by others evaluating EOC risk in relation to ovulatory stimulation [14–16, 19]. In a combined analysis evaluating the use of fertility agents and the risk of BOT and EOC separately, the risk of BOT was stronger than that for EOC [14, 22], and this was also observed elsewhere [41]. Because there are inconsistent findings in the literature and because of the complexity separating various factors causing infertility, it is unlikely that fertility agents alone contribute a large increased risk for the development of EOC.
- Ovarian epithelial dysplasia was also described after prophylactic oophorectomies for genetic risk and was linked to be risk factor for EOC through the incessant ovulation theory. The data reported from France revealed a higher ovarian dysplasia score in the ovulation induction group than in the control group, although the number of cases in this study is low. They also found a relationship between the number of ovulation-induced cycles and the severity of ovarian dysplasia (dose-effect) and a relationship between time after the end of ovulation induction (over 7 years) and the severity of ovarian dysplasia (time-effect) [48].

Hormone replacement therapy (HRT)

- HRT is mainly indicated to alleviate climacteric symptoms as well as to strengthen bone. Previous epidemiological findings on HRT and the risk of EOC are contradictory. In a few studies HRT appeared to reduce the risk of EOC [49, 50], whereas other studies demonstrated no associations [14, 16, 51], or moderately increased risks of EOC among HRT users [10, 13, 17, 18, 23]. In several studies where a positive association between HRT ever-use and EOC risk was seen, no clear trends with duration appeared [17, 18]. However, other studies indicated elevated EOC risks after longer durations of HRT use [10, 23, 52–54], and excess risk that declined after discontinuation of use [54, 55].
- In a recent well-conducted cohort study of 44,241 US women, a RR for ovarian cancer of 1.6 (95%CI 1.2–2.0) was reported among ever-users compared with never-users of estrogen replacement therapy (ERT) [56], and the largest risk was seen among those who had used ERT for 20 years or more (RR 3.2; 95%CI 1.7–5.7).
- One of the studies evaluated the risk of EOC in relation to sequential or continuous progestin regimens in HRT [57]. This study demonstrated an increased risk of EOC among ever-users compared with never-users of HRT containing estrogens opposed by sequential progestins(OR 1.53; 95%CI 1.15–2.05), and the highest risks were observed among those who had used this type of HRT in excess of 10 years. Ever-use of estrogens continuously combined with progestins was unrelated to EOC risk (OR 1.02; 95%CI 0.73–1.43). In the Women's Health Initiative (WHI) study, the hazard ratio for the increased risk of ovarian cancer was 1.58 (95% CI 0.74–3.24) in women who were randomly assigned to either a fixed combination of 0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate or the placebo [58]. The risk estimate was based upon 32 incident ovarian cancers (20 in the treatment group and 12 in the placebo group) that occurred during a mean follow-up time of 5.6 years. Although statistically not significant, the WHI authors suggested that the risk of ovarian cancer is increased among users of this type of HRT regimen. In a population-based study in Washington State, 812 women with ovarian cancer and 1313 controls were interviewed about the use of HRT and other characteristics. The risk of EOC was increased among current or recent (within the last three years) users of unopposed estrogen for five or more years (OR 1.6, 95%CI 1.1–2.5 and OR 1.8, 95%CI 0.8–3.7, respectively). However, no increase in risk was noted among women who used combined estrogen and progestins therapy regardless of duration (OR 1.1, 95%CI 0.8–1.5) [59].
- Some studies suggest that the effect of ERT on EOC risk is modified by hysterectomy, with an excess risk of EOC among ERT users present only among women with an intact uterus but not in hysterectomized women [14, 55, 57]. However, the US cohort data reported an elevated risk of EOC among both hysterectomized and nonhysterectomized subjects [56]. The responsiveness to HRT may differ depending on the histological type of EOC, serous being the most common, followed by mucinous and then endometroid and clear cell. Elevated risks of the less common endometrioid EOC, in particular, have been reported by most [10, 23, 52, 55, 57, 60] but not all studies [14, 17, 49–51] examining this association. Some [23, 52, 57] but not

other [49–51, 55] studies indicated an elevated risk of serous EOC among ERT users, while most previous research indicates that HRT is unrelated to the risk of mucinous EOC [23, 49, 52, 55], although positive associations have been observed [51, 57].

- In one of these studies, based on a cohort of more than 200,000 postmenopausal women, an RR of 2.20 (95%CI 1.53–3.17) for fatal EOC appeared among those who had used ERT longer than 10 years compared with nonusers [54]. However, it has also been reported that HRT is not related to the risk of recurrent EOC [61]. Only a handful of studies have reported no association between the use of HRT and the risk of BOT [19, 20, 22, 23].
- The potential carcinogenic effect of HRT compounds could be explained by retrograde bleeding through the Fallopian tubes [62, 63]. This suggestion is supported by the absence of an elevated risk of EOC among hysterectomized women using ERT [55, 57, 60]. An additional, perhaps more likely, mechanism to explain an increased risk of EOC among HRT users includes a direct hormonal action on steroid receptors [7]. Estrogen is a well-known endometrial-lining carcinogen. Although the explanation for the increased risk with HRT/ERT is not clear, this should nevertheless be considered as part of the overall discussion of risk and benefits of treatment.

Gynecologic-related condition

Gynecologic surgery

- Bilateral oophorectomy will reduce the risk of ovarian cancer almost completely, but for obvious reasons, this is not performed routinely. In the case of a genetic predisposition such as inherited BRCA-1, BRCA-2 or HNPCC mutations, prophylactic oophorectomy is life-saving as the risk of future ovarian cancer is as high as 50%. In the case of routine hysterectomy for benign indications, the question always arises: should the ovaries be removed. The benefit would be a nearly complete elimination of the risk of future ovarian cancer and future operations for benign adnexal conditions. As women approach menopause, it seems reasonable to consider removal of the ovaries at the time of hysterectomy. However, some studies suggest other medical benefits to leaving the ovaries intact even at the time of menopause that may outweigh the reduction in cancer and future operation risks. This may be due to hormones. Although menses cease at menopause, there continues to be an ever diminishing secretion of hormones that may have a beneficial effect.
- Almost all epidemiological studies that examined the association between tubal ligation and EOC risk support a protective effect with observed risk reductions from 10% to 80% [11, 13, 17, 23, 64–66]. Prospective data from the Nurses Health Study on a cohort of 121,700 female nurses (30–55 years) showed a statistically significant 67% reduced risk of EOC among nurses who had tubal ligation compared to those without this procedure [66]. The reduced risks of EOC after tubal ligation also persisted across all levels of parity in this study. Furthermore, the protective effect after tubal ligation has been reported to persist up to 20 years after the surgery [64, 65]. It appears that most common surgical sterilization methods are equally protective [65]. Tubal ligation has also been observed to reduce the risk of BOT, although because of a limited number of cases these results are often statistically not significant [20, 22]. The majority of studies

where hysterectomy was assessed in relation to EOC risk have demonstrated an inverse association [13, 17, 33, 65, 66]. The magnitude of the protection against EOC seems somewhat weaker compared with the protection afforded by tubal ligation. In the Nurses Health study the risk of EOC decreased by 33% after hysterectomy [66]. In contrast with tubal ligation and hysterectomy, fewer reports have examined unilateral oophorectomy in relation to EOC and BOT risks. A reduced risk of EOC appeared after unilateral oophorectomy in some investigations [13, 33, 49, 67], whereas the opposite was found in another study [68], and no associations were reported by others [17]. A population-based case–control study with personal phone interviews of ovarian cancer patients found an increased risk of borderline mucinous ovarian tumors associated with a history of ovarian cysts (OR = 1.7, 95%CI 1.0–2.8), but did not vary notably according to receipt of subsequent ovarian surgery. The risk of invasive EOC, in this study, was slightly increased among women with a cyst who had no subsequent ovarian surgery, it was reduced when a cyst diagnosis was followed by surgery (OR = 0.6, 95%CI 0.4–0.9) [69].

Endometriosis

- Endometriosis is a common medical condition where endometrial tissue is present outside the uterine cavity, preferentially in the cul-de-sac and on the ovarian surface [70]. The hormonally regulated lesions of endometriosis may trigger a local inflammatory reaction with activation of macrophages, release of cytokines and elevation of growth factors [70]. Several studies have linked endometriosis to an increased risk of EOC [70, 71]. Several clinical series also reported the coexistence of endomtriosis and EOC [72], particularly endometrioid [71, 72] and clear-cell EOC [71]. One study reported threefold increase risk of endometrioid and clear cell invasive tumors in women with a history of endometriosis, with a lesser risk increase among women who underwent subsequent ovarian surgery [69]. Endometriosis is also linked to elevated risks for ovarian cancer with standardized incidence ratios (SIR) of 1.37, endocrine tumors, renal cancer, thyroid cancer, brain tumors, malignant melanoma and breast cancer, as well as a reduced risk of cervical cancer in National Swedish Inpatient Data [73]. Endogenous or exogenous hyperestrogenism was positively related to the risk of development of cancer from endometriosis [70, 74]. One study at the University of Hawaii found 95% of clear cell and endometriod ovarian cancers to be histologically associated with endometriosis further suggesting the pre-malignant nature of some cases of endometriosis and forming an additional theory for the reduction of risk of these cancers with oral contraceptives.

Pelvic inflammatory disease (PID)

- PID includes endometritis, salpingo-oophoritis and tubo-ovarian abscess formation. A limited number of epidemiological studies have focused on the associations between PID and the risk of EOC [75, 76]. Some of these studies found positive associations between PID and the risk of EOC [76] while others found no effects [16, 65, 77]. A Canadian Study reported an increased EOC risk among women with

one compared to no episodes of PID (OR 95% CI 1.0–2.1) [76] and the positive association between PID and EOC risk was stronger if PID had occurred at an early age, if the women were nulliparous, infertile, or had experienced recurrent PID episodes. This study also reported similar risk estimates for EOC and BOT in relation to PID.

Polycystic ovarian syndrome

- Common clinical presentations of polycystic ovarian syndrome (PCOS) include obesity, hirsutism, infertility and menstrual abnormalities. Obese women with PCOS are at an increased risk of uterine endometrial cancer [77], but the relationship between PCOS and EOC risk is less extensively evaluated. Elevated risks of EOC appeared among women with PCOS (OR 2.5; 95%CI 1.1–5.9) and the associations were stronger among those who had not used OCs or were lean [78]. Other study found PCOS unrelated to EOC [77].

Environmental risk factors

- Genital use of talcum powder has been extensively investigated as a potential risk factor for ovarian cancer. A meta-analysis reported an approximately 30% increase in the risk of total EOC with regular genital exposure to talc [79], and several studies have suggested a stronger association with the serous or serous invasive histologic subtype [80, 81]. Talc is structurally similar to asbestos, and studies have suggested that there are histologic similarities between serous adenocarcinomas and the mesotheliomas seen in asbestos exposure. These facts may explain findings of an increased risk of serous tumors in talc powder users [82]. Talc also can induce granulomas and other inflammatory responses in vivo [83] and a recent study found that exposing human ovarian stromal and epithelial cells to talc resulted in increased cell proliferation and neoplastic transformation of cells [84]. Talc also appears to increase cellular production of reactive oxygen species. Animal studies also demonstrated that talc migrates from the vagina through the peritoneal cavity to the ovaries. Talc then may stimulate the entrapment of the ovarian surface epithelium, causing a reaction similar to the reaction that occurs during ovulation. A new study is attempting to relate genetic factors such as variants of the glutathione S-transferase M1(GSTM1) and N-acetyltransferase 2(NAT2) to the association between talc exposure and ovarian cancer risk [85]. Although there was no clear evidence of the interaction of these genes, these results suggest that women with certain genetic variants may have a higher risk of ovarian cancer associated with genital talc use.
- Cigarette smoking may be a risk factor for ovarian cancer, although its role is controversial. Some studies reported smoking to increase the risk of mucinous tumors [86, 87] but some studies failed to find a significant correlation with ovarian cancer risk [88]. Although smoking doubles the risk of mucinous ovarian cancers in meta-analyses, this study showed that smoking cessation returned the risk to that of never having smoked within 20 to 30 years [89].
- Dietary factors may also relate to the risk of ovarian cancer, but the evidence remains controversial. A recent study reviewed the intake of red meat which suggested an increased risk of ovarian cancer with an OR of 1.53 for the highest intake compared to women in the lowest

quintile [90]. A study from Italy reported that a diet containing bread and pasta is associated with an increased risk of breast and ovarian cancer (OR 1.21 for ovarian cancer). In contrast, the consumption of fruits and vegetables was protective against ovarian cancer with OR = 0.81 [91]. Diets high in fiber, carotene, and vitamins seem to be protective [92, 93]. Vitamins A, C, D, and E have, for the most part, shown some reduced risk of ovarian cancer [94, 95]. There were pros and cons of fruit and vegetable consumption in association with reduced risk of ovarian cancer [94] versus no effect on risk reduction [96, 97].

- Several studies reported an inverse association between dietary vitamin D [98], sunlight exposure [99] and ovarian cancer. The observation that vitamin D and it's synthetic analogues inhibit growth and induce apoptosis in ovarian cells in culture and in animal models of ovarian cancer [100–102] provide further plausibility to this hypothesis. The proposed mechanism for the role of vitamin D in carcinogenesis involves regulation of differentiation and proliferation of cancer cells possibly by influencing cell cycle regulatory proteins [103]. Down-regulation of telomerase activity by vitamin D might be another component of the ovarian cancer cellular growth suppression [101]. The vitamin D receptor (VCR) is a nuclear transcription factor that mediates most of the actions of vitamin D [104]. In an animal study, VDR-null mice exhibited gonadal insufficiency, had reduced aromatase gene expression and activity, and had elevated serum levels of luteinizing and follicle-stimulating hormones [105]. In humans, a study revealed evidence that polymorphisms in VDR genes might influence ovarian cancer susceptibility [104].
- Studies on the influence of alcohol intake showed conflicting data, with several studies reporting no association between total intake and ovarian cancer [106, 107]. Although one study noted and association between heavy consumption of alcohol to and increased risk of mucinous ovarian cancer [108].
- Caffeine intake has been reported to increase the risk of ovarian cancer in premenopausal women [109], to have no association [110] and to decrease the risk of ovarian cancer [111]. The consumption of tea, specifically green and black tea, has been shown to reduce the risk of EOC in a dose–response manner [112]. The proposed mechanisms of protection include antioxidant activity, changes in cell signaling pathways, induction of apoptosis, and the possibility of the modulation of endogenous hormones [113].
- Overweight (BMI 25–29.9) and obesity (BMI $\geq$ 30) in early adulthood was also associated with an increased risk of ovarian cancer with pooled OR = 1.5 among case–control analyses from a meta-analysis from Australia [114]. There was no evidence that the association varied for the different histological subtypes of ovarian cancer.

Genetic risk factors

- Considering all the factors mentioned above, none contributes more to the future risk of EOC as do genetic, specifically hereditary, factors.
- Mutated high-penetrance genes such as the breast-ovarian cancer genes BRCA1/2 have been shown to increase the risk of EOC, particularly serous carcinoma. Approximately 10% of ovarian cancers are hereditary, with BRCA1 and BRCA2 explaining the majority (approximately 90%) of hereditary ovarian cancer cases. The lifetime risk varies between 15% and 66%, suggesting the existence of modi-

fying genetic or environmental factors [115]. Ovarian cancer has also been associated strongly with Lynch Syndrome, (HNPCC), and less so with basal cell nevus (Gorlin) syndrome, and multiple endocrine neoplasia type 1 (MEN1) [116].

- Low-penetrance susceptibility genes have been shown to influence the risk of different histologic types of EOCs. For example, the glutathione S-transferase M1 (GSTM1) null genotype has been associated with an increased risk of endometrioid or clear cell invasive cancer [76, 117, 118]. In addition, while possession of the A2 variant of the P450c17 alpha gene(CYP17) appeared to increase the risk for all types of ovarian cancer, possession of the Val/Met variant of catechol-o-methyltransferase (COMT) decreased the risk for mucinous tumors [118]. There are also data relating the risks of EOC to differences in DNA sequences among individuals, groups, or populations. For example, paraoxonase I genes are involved in formation of oxygen free radicals in cells [119] or estrogen receptor beta genes (ESR2) [120] which mediate estrogen-induced apoptosis both showing an association with an increased risk of ovarian cancer due to defects of the genes in certain populations. A small population-based case–control study from Hawaii also showed that genetic variations of CYP19A1 may influence susceptibility to ovarian cancer among caucasian and Japanese women, by 10–20% increases in estrogen production among postmenopausal women [121].

Conclusion

- Epidemiologic studies are among the first clues in the effort to detect risk factors associated with cancer. These studies form the scientific foundation from which theory development, hypothesis testing and ultimately a better understanding and treatment of cancer arises. The current understanding of ovarian cancer is no exception. In fact, it was rigorous epidemiologic, family history, and genetic studies that led to the identification of the BRCA 1 and BRCA 2 genes enabling us to prevent the almost certain occurrence of a cancer. The pathogenesis of ovarian cancer is a complex process, which certainly involves host genetic factors influenced by hormones, inflammation, pregnancy and other environmental factors. At this point in time, the most important modifiable protective factors include identifying a hereditary cancer syndrome with subsequent prophylaxis, avoidance of genital talc, treatment of endometriosis, and the use of oral contraceptives.

References and Recommended Reading

1. Jekmal A, Siegel R, Ward E, *et al.*: **Cancer statistics, 2008.** *CA Cancer J Clin* 2008, **58:**71–96.
2. Hanna L, Adams M: **Prevention of ovarian cancer.** *Best Pract Res Clin Obstet Gynaecol* 2006, **20:**339–362.
3. Mok SC, Kwong J, Welch WR, *et al.*: **Etiology and pathogenesis of epithelial ovarian cancer.** *Dis Markers* 2007, **23:**367–376.
4. Fathalla MF: **Incessant ovulation—a factor in ovarian neoplasia?** *Lancet* 1971, **2:**163.
5. Riman T, Persson I, Nilsson S: **Hormonal aspects of epithelial ovarian cancer: review of epidemiological evidence.** *Clin Endocrinol* 1998, **49:**695–707.
6. Zheng H, Kavanagh JJ, Hu W, *et al.*: **Hormonal therapy in ovarian cancer.** *Int J Gynecol Cancer* 2007, **17:**325–338.
7. Risch HA: **Hormonal etiology of epithelial ovarian cancer with a hypothesis concerning the role of androgen and progesterone.** *J Natl Cancer Inst* 1998, **90:**1774–1786.
8. Ness RB, Griss JA, Cottreau C, *et al.*: **Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer.** *Epidemiology* 2000, **11:**111–117.
9. Cramer DW, Barbieri RL, Fraer AR, Harlow BL: **Determinants of early follicular phase gonadotrophin**

and estradiol concentrations in women of late reproductive age. *Hum Reprod* 2002, **17:**221–227.

10. Cramer DW, Hutchison GB, Welch WR, *et al.*: **Determinants of ovarian cancer risk. I. Reproductive experiences and family history.** *J Natl Cancer Inst* 1983, **71:**711–716.
11. Wittenberg L, Cook LS, Rossing MA, Weiss NS: **Reproductive risk factors for mucinous and nonmucinous epithelial ovarian cancer.** *Epidemiology* 1999, **10:**761–763.
12. Adami HO, Hsieh CC, Lambe M, *et al.*: **Parity, age at first childbirth, and risk of ovarian cancer.** *Lancet* 1994, **344:**1250–1254.
13. Riman T, Dickman PW, Nilsson S, *et al.*: **Risk factors for invasive epithelial ovarian cancer: result from a Swedish case-control study.** *Am J Epidemiol* 2002, **156:**363–373.
14. Whittemore AS, Harris R, Itnyre J: **Characteristics relating to ovarian cancer risk; collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group.** *Am J Epidemiol* 1992, **136:**1184–1203.
15. Risch HA, Marrett LD, Howe GR: **Parity, contraception, infertility, and the risk of epithelial ovarian cancer.** *Am J Epidemiol* 1994, **140:**585–597.
16. Purdie D, Green A, Bain C, *et al.*: **Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group.** *Int J Cancer* 1995, **62:**678–684.
17. Booth M, Beral V, Smith P: **Risk factors for ovarian cancer: a case-control study.** *Br J Cancer* 1989, **60:**592–598.
18. Polychronopoulou A, Tzonou A, Hsieh CC, *et al.*: **Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer.** *Int J Cancer* 1993, **55:**402–407.
19. Riman T, Dickman PW, Nilsson S, *et al.*: **Risk factors of epithelial borderine ovarian tumors: results of a Swedish case-control study.** *Gynecol Oncol* 2001, **83:**575–585.
20. Harlow BL, Weiss NS, Roth GJ, *et al.*: **Case-control study of borderline ovarian tumors: reproductive history and exposure to exogenous female hormones.** *Cancer Res* 1988, **48:**5849–5852.
21. Parazzine F, Restelli C, La Vecchia C, *et al.*: **Risk factors for epithelial ovarian tumours of borderline malignancy.** *Int J Epidemiol* 1991, **20:**871–877.
22. Harris R, Whittemore AS, Itnyre J: **Characteristic relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. III. Epithelial tumors of low malignant potential in white women. Collaborative Ovarian Cancer Group.** *Am J Epidemiol* 1992, **136:**1204–1211.
23. Risch HA, Marrett LD, Jain M, Howe GR: **Differences in risk factors for epithelial ovarian cancer by histologic type: results of a case-control study.** *Am J Epidemiol* 1996, **144:**363–372.
24. Cnattingius S, Eloranta S, Adami HO, *et al.*: **Placental weight and risk of invasive epithelial ovarian cancer with an early age of onset.** *Cancer Epidemiol Biomarkers Prev* 2008, **17:**2344–2349.
25. Mucci LA, Dickman PW, Lambe M, *et al.*: **Gestational age and fetal growth in relation to maternal ovarian cancer risk in a Swedish cohort.** *Cancer Epidemiol Biomarkers Prev* 2007, **16:**1828–1832.
26. Munstedt K, Steen J, Knauf AG, *et al.*: **Steroid hormone receptors and long term survival in invasive ovarian cancer.** *Cancer* 2000, **89:**1783–1791.
27. Bu SZ, Yin DL, Ren XH, *et al.*: **Progesterone induces apoptosis and up-regulation of p53 expression in human ovarian carcinoma cell lines.** *Cancer* 1997, **79:**1944–1950.
28. Lukanova A, Lundin E, Toniolo P, *et al.*: **Circulating levels of insulin-like growth factor-I and risk of ovarian cancer.** *Int J Cancer* 2000, **101:**549–554.
29. Danforth KN, Tworoger SS, Hecht JL, *et al.*: **Breastfeeding and risk of ovarian cancer in two prospective cohorts.** *Cancer Causes Control* 2007, **18:**517–523.
30. Hankinson SE, Colditz GA, Hunter DJ, *et al.*: **A prospective study of reproductive factors and risk of epithelial ovarian cancer.** *Cancer* 1995, **76:**284–290.
31. Moorman PG, Calingaert B, Palmieri RT, *et al.*: **Hormonal risk factors for postmenopausal women.** *Am J Epidemiol* 2008, **167:**1059–1069.
32. Hankinson SE, Colditz GA, Hunter DJ, *et al.*: **A quantitative assessment of oral contraceptive use and risk of ovarian cancer.** *Obstet Gynecol* 1992, **80:**708–714.
33. Rosenberg L, Palmer JR, Zauber AG, *et al.*: **A case-control study of oral contraception use and invasive epithelial ovarian cancer.** *Am J Epidemiol* 1994, **139:**654–655.
34. **The Cancer and Steroid Hormone (CASH) Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. The reduction in risk of ovarian cancer associated with oral-contraceptive use**. *N Engl J Med* 1987, **316:**650–655.
35. Stanford JL: **Oral contraceptives and neoplasia of the ovary.** *Contraception* 1991, **43:**543–556.
36. Franceschi S, Parazzini F, Negri E, *et al.*: **Pooled analysis of 3 European case-control studies of epithelial ovarian cancer. III. Oral contraceptive use.** *Int J Cancer* 1991, **49:**61–65.
37. Wernli KJ, Newcomb PA, Hampton JM, *et al.*: **Inverse association of NSAID use and ovarian cancer in relation to oral contraceptive use and parity.** *Br J Cancer* 2008, **98:**1781–1783.
38. Bamford PN, Seele SJ: **Uterine and ovarian carcinoma in a patient receiving gonadotropin therapy. Case report.** *Br J Obstet Gynaecol* 1982, **89:**962–964.
39. Bristow RE, Karlan BY: **Ovulation induction, infertility, and ovarian cancer risk.** *Fertil Steril* 1996, **66:**499–507.
40. Shushan A, Paltiel O, Iscovich J, *et al.*: **Human menopausal gonadotropin and the risk of epithelial ovarian cancer.** *Fertil Steril* 1996, **65:**13–18.
41. Venn A, Watson L, Lumley J, *et al.*: **Breast and ovarian cancer incidence after infertility and in vitro fertilization.** *Lancet* 1995, **346:**995–1000.

42. Franceschi S, La Vecchia C, Negri E, *et al.*: **Fertility drugs and risk of epithelial ovarian cancer in Italy.** *Hum Reprod* 1994, **9:**1673–1675.
43. Calderon-Margalit R, Friedlander Y, Yanetz R, *et al.*: **Cancer risk after exposure to treatments for ovulation induction.** *Am J Epidemiol* 2009, **169:**365–375 Epub 2008 Nov 26.
44. Mosgaard BJ, Lidegaard O, Kjaer SK, *et al.*: **Infertility, fertility drugs, and invasive ovarian cancer: a case-control study.** *Fertil Steril* 1997, **67:**1005–1012.
45. Brinton LA, Melton LJ, Malkasian GD, *et al.*: **Cancer risk after evaluation for infertility.** *Am J Epidemiol* 1989, **129:**712–722.
46. Rossing MA, Daling JR, Weiss NS, *et al.*: **Ovarian tumors in a cohort of infertile women.** *N Engl J Med* 1994, **331:**771–776.
47. Ron E, Lunenfeld B, Menczer J, *et al.*: **Cancer incidence in a cohort of infertile women.** *Am J Epidemiol* 1987, **125:**780–790.
48. Chene G, Penault-Llorca F, Le Bouedec G, *et al.*: **Ovarian epithelial dysplasia after ovulation induction: time and dose effects.** *Hum Reprod* 2009, **24:**132–138.
49. Hartge P, Hoover R, McGowan L, *et al.*: **Menopause and ovarian cancer.** *Am J Epidemiol* 1988, **127:** 990–998.
50. Hempling RE, Wong C, Piver MS, *et al.*: **Hormone replacement therapy as a risk factor for epithelial ovarian cancer: results of a case-control study.** *Obstet Gynecol* 1997, **89:**1012–1016.
51. Kaufman DW, Kelly JP, Welch WR, *et al.*: **Noncontraceptive estrogen use and epithelial ovarian cancer.** *Am J Epidemiol* 1989, **130:**1142–1151.
52. Risch HA: **Estrogen replacement therapy and risk of epithelial ovarian cancer.** *Gynecol Oncol* 1996, **63:**254–257.
53. Garg PP, Kerlikowske K, Subak L, Grady D: **Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis.** *Obstet Gynecol* 1998, **92:**472–479.
54. Rodriguez C, Patel AV, Calle EE, *et al.*: **Estrogen replacement therapy and ovarian cancer mortality in a large prospective study of US women.** *J Am Med Assoc* 2001, **285:**1460–1465.
55. Purdie DM, Bain CJ, Siskind C, *et al.*: **Hormone replacement therapy and risk of epithelial ovarian cancer.** *Br J Cancer* 1999, **81:**559–563.
56. Lacey JV, Mink PJ, Lubin JH, *et al.*: **Menopausal hormone replacement therapy and risk of ovarian cancer.** *J Am Med Assoc* 2002, **288:**334–341.
57. Riman T, Dickman PW, Nilsson S, *et al.*: **Hormone replacement therapy and the risk of invasive epithelial ovarian cancer in Swedish women.** *J Natl Cancer Inst* 2002, **94:**497–505.
58. Anderson GL, Judd HL, Kaunitz AM, *et al.*: **Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women's Health Initiative Randomized Trial.** *J Am Med Assoc* 2003, **290:**1739–1748.
59. Rossing MA, Cushing-Haugen KL, Wicklund KG, *et al.*: **Menopausal hormone therapy and risk of epithelial ovarian cancer.** *Cancer Epidemiol Biomarkers Prev* 2007, **16:**2548–2556.
60. Riman T: **Hormone replacement therapy and epithelial ovarian cancer: is there an association?.** *J Br Menopause Soc* 2003, **2:**61–68.
61. Eeles RA, Tan S, Wiltshaw E, *et al.*: **Hormone replacement therapy and survival after surgery for ovarian cancer.** *Br Med J* 1991, **302:**259–262.
62. Cramer DW, Xu H: **Epidemiologic evidence of uterine growth factors in the pathogenesis of ovarian cancer.** *Ann Epidemiol* 1995, **5:**301–314.
63. Halme J, Hammond MG, Hulka JF, *et al.*: **Retrograde menstruation in healthy women and in patients with endometriosis.** *Obstet Gynecol* 1984, **64:**151–154.
64. Miracle-McMahill HL, Calle EE, Kosinski AS, *et al.*: **Tubal ligation and fatal ovarian cancer in a large prospective cohort study.** *Am J Epidemiol* 1997, **145:**349–357.
65. Green A, Purdie D, Bain C, *et al.*: **Tubal sterilization, hysterectomy and decreased risk of ovarian cancer.** *Int J Cancer* 1997, **71:**948–951.
66. Hankinson SE, Hunter DJ, Colditz GA, *et al.*: **Tubal ligation, hysterectomy and risk of ovarian cancer, a prospective study.** *J Am Med Assoc* 1993, **270:**2813–2818.
67. Beard CM, Hartmann LC, Atkinson EJ, *et al.*: **The epidemiology of ovarian cancer: a population-based study in Olmsted County, Minnesota, 1935–1991.** *Ann Epidemiol* 2000, **10:**14–23.
68. Kreiger N, Sloan M, Cotterchio M, Parsons P: **Surgical procedures associated with risk of ovarian cancer.** *Int J Epidemiol* 1997, **26:**710–715.
69. Rossing MA, Cushing-Haugen KL, Wicklund KG, *et al.*: **Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery.** *Cancer Causes Control* 2008, **19:**1357–1364.
70. Brinton LA, Gridley G, Persson I, *et al.*: **Cancer risk after a hospital discharge diagnosis of endometriosis.** *Am J Obstet Gynecol* 1997, **176:**572–579.
71. Ogawa S, Kaku T, Amada S, *et al.*: **Ovarian endometriosis associated with ovarian carcinoma: a clinicopathological and immunohistochemical study.** *Gynecol Oncol* 2000, **77:**298–304.
72. Takahashi K, Kurioka H, Irikoma M, *et al.*: **Benign or malignant ovarian neoplasms and ovarian endometriomas.** *J Am Assoc Gynecol Laparosc* 2001, **8:**278–284.
73. Melin A, Sparen P, Bergqvist A: **The risk of cancer and the role of parity among women with endometriosis.** *Hum Reprod* 2007, **22:**3021–3026.
74. Zanetta GM, Webb MJ, Li H, Keeney GL.: **Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis.** *Gynecol Oncol* 2000, **79:**18–22.
75. Risch HA, Howe GR: **Pelvic inflammatory disease and the risk of epithelial ovarian cancer.** *Cancer Epidemiol Biomarkers Prev* 1995, **4:**447–451.
76. Parazzini F, La Vecchia C, Negri E, *et al.*: **Pelvic inflammatory disease and risk of ovarian cancer.** *Cancer Epidemiol Biomarkers Prev* 1996, **5:**667–669.

77. Balen A: **Polycystic ovary syndrome and cancer.** *Hum Reprod Update* 2001, **7:**522–525.
78. Schuldkraut JM, Schwingl PJ, Bastos E, *et al.*: **Epithelial ovarian cancer risk among women with polycystic ovary syndrome.** *Obstet Gynecol* 1996, **88:**554–559.
79. Huncharek M, Geschwind JF, Kupelnick B: **Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies.** *Anticancer Res* 2003, **23:**1955–1960.
80. Cook LS, Kamb ML, Weiss NS: **Perineal powder exposure and the risk of ovarian cancer.** *Am J Epidemiol* 1997, **145:**459–465.
81. Gertig DM, Hunter DJ, Cramer DW, *et al.*: **Prospective study of talc use and ovarian cancer.** *J Natl Cancer Inst* 2000, **92:**249–252.
82. Mills PK, Riodan DG, Cress RD, Young HA: **Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California.** *Int J Cancer* 2004, **112:**458–464.
83. Harlow BL, Hartge PA: **A review of perineal talc exposure and risk of ovarian cancer.** *Regul Toxicol Pharmacol* 1995, **21:**254–260.
84. Buz'Zard AR, Lau BH: **Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures.** *Phytother Res* 2007, **21:**579–586.
85. Gates MA, Tworoger SS, Terry KL, *et al.*: **Talc use, variants of the GSTM1, GSTT, and NAT2 genes, and risk of epithelial ovarian cancer.** *Cancer Epidemiol Biomarkers Prev* 2008, **17:**2436–2444.
86. Soegaard M, Jensen A, Hogdall E, *et al.*: **Different risk factor profiles for mucinous and non-mucinous ovarian cancer: result from the Danish MALOVA Study.** *Cancer Epidemiol Biomarkers Prev* 2007, **16:**1160–1166.
87. Marchbanks PA, Wilson H, Bastos E, *et al.*: **Cigarette smoking and epithelial ovarian cancer by histology type.** *Obstet Gynecol* 2000, **95:**255–260.
88. Riman T, Dickman PW, Nilsson S, *et al.*: **Some lifestyle factors and the risk of invasive epithelial ovarian cancer in Swedish women.** *Eur J Epidemiol* 2004, **19:**1011–1019.
89. Jordan SJ, Whiteman DC, Purdie DM, *et al.*: **Does smoking increase risk of ovarian cancer? A systemic review.** *Gynecol Oncol* 2006, **103:**1122–1129.
90. Bosetti C, Negri E, Franceschi S, *et al.*: **Diet and ovarian cancer risk: a case-control study in Italy.** *Int J Cancer* 2001, **93:**911–915.
91. Edefonti V, Randi G, Decarli A, *et al.*: **Clustering dietary habits and the risk of breast and ovarian cancers.** *Ann Oncol* 2009, **20:**581–590 Epub 2008 Oct 7.
92. Zhang M, Lee AH, Binns CW: **Reproductive and dietary risk factors for epithelial ovarian cancer in China.** *Gynecol Oncol* 2004, **92:**320–326.
93. Bidoli E, La Vecchia C, Montella M, *et al.*: **Nutrient intake and ovarian cancer: an Italian case-control study.** *Cancer Causes Control* 2002, **13:**255–261.
94. McCann SE, Moysich KB, Mettlin C: **Intakes of selected nutrients and food groups and risk of ovarian cancer.** *Nutr Cancer* 2001, **39:**19–28.
95. Fleischauer AT, Olson SH, Mignone L, *et al.*: **Dietary antioxidants, supplements and risk of epithelial ovarian cancer.** *Nutr Cancer* 2001, **40:**92–98.
96. Mommers M, Schouten LJ, Goldbohm RA, van den Brandt PA: **Consumption of vegetables and fruits and risk of ovarian cancer.** *Cancer* 2005, **104:**1512–1519.
97. Koushik A, Hunter DJ, Spiegelman D, *et al.*: **Fruits and vegetables and ovarian cancer risk in a pooled analysis of 12 cohort studies.** *Cancer Epidemiol Biomarkers Prev* 2005, **14:**2160–2167.
98. Salazar-Martinez E, Lazcano-Ponce EC, Gonzalez Lira-Lira G, *et al.*: **Nutritional determinants of epithelial ovarian cancer risk: a case-control study in Mexico.** *Oncology* 2002, **63:**151–157.
99. Garland CF, Mohr SB, Gorham ED, *et al.*: **Role of ultraviolet B irradiance and vitamin D in prevention of ovarian cancer.** *Am J Prev Med* 2006, **31:** 512–514.
100. Saunders DE, Christensen C, Lawrence WD, *et al.*: **Receptors for 1,25-dihydroxyvitamin D3 in gynecologic neoplasms.** *Gynecol Oncol* 1992, **44:**131–136.
101. Jiang F, Bao J, Li P, *et al.*: **Induction of ovarian cancer cell apoptosis by 1,25-dihydroxyvitamin D3 through the down regulation of telomerase.** *J Biol Chem* 2004, **279:**53213–53221.
102. Zhang X, Jiang F, Li P, *et al.*: **Growth suppression of ovarian cancer xenografts in nude mice by vitamin D analogue EB1089.** *Clin Cancer Res* 2005, **11:** 323–328.
103. Holick MF: **Vitamin D: its role in cancer prevention and treatment.** *Prog Biophys Mol Biol* 2006, **92:**49–59.
104. Lurie G, Wilkens LR, Thompson PJ, *et al.*: **Vitamin D receptor gene polymorphism and epithelial ovarian cancer risk.** *Cancer Epidemiol Biomarkers Prev* 2007, **16:**2566–2571.
105. Kinuta K, Tanaka H, Moriwake T, *et al.*: **Vitamin D is an important factor in estrogen biosynthesis of both female and male gonad.** *Endocrinology* 2000, **141:**1317–1324.
106. Chang ET, Canchola AJ, Lee VS, *et al.*: **Wine and other alcohol consumption and risk of ovarian cancer in the California Teachers Study cohort.** *Cancer Causes Control* 2007, **18:**91–103.
107. Peterson NB, Trentham-Dietz A, Newcomb PA: **Alcohol consumption and ovarian cancer in a population-based case-control study.** *Int J Cancer* 2006, **119:**2423–2427.
108. Modugno F, Ness RB, Allen GO: **Alcohol consumption and the risk of mucinous and nonmucinous epithelial ovarian cancer.** *Obstet Gynecol* 2003, **102:**1336–1343.
109. Kuper H, Titus-Ernstoff L, Harlow BL: **Population based study of coffee, alcohol and tobacco use and risk of ovarian cancer.** *Int J Cancer* 2000, **88:**313–318.
110. Larsson SC, Wolk A: **Coffee consumption is not associated with ovarian cancer incidence.** *Cancer Epidemiol Biomarkers Prev* 2005, **14:**2273–2274.

111. Jordan SJ, Purdie DM, Green AC, Webb PM: **Coffee, tea, and caffeine and risk of epithelial ovarian cancer.** *Cancer Causes Control* 2004, **15:**359–365.
112. Larsson SC, Wolk A: **Tea consumption and ovarian cancer risk in a population-based cohort.** *Arch Intern Med* 2005, **165:**2683–2686.
113. Rieck G, Fiander A: **The effect of lifestyle factors on gynaecological cancer.** *Best Pract Res Clin Obstet Gynaecol* 2006, **20:**227–251.
114. Olsen CM, Green AC, Whiteman DC, *et al.*: **Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis.** *Eur J Cancer* 2007, **43:**690–709.
115. Antoniou AC, Gayther SA, Stratton JF, *et al.*: **Risk models for familial ovarian and breast cancer.** *Genet Epidemiol* 2000, **18:**173–190.
116. Lindor NM, McMaster ML, Lindor CJ, Greene MH: **Concise handbook of familial cancer susceptibility syndromes—second edition.** *J Natl Cancer Inst Monogr* 2008, **38:**1–93.
117. Spurdle AB, Hoppor JL, Chen X, *et al.*: **The steroid 5 alpha-reductase type II TA repeat polymorphism is not associated with risk of breast or ovarian cancer in Australian women.** *Cancer Epidemiol Biomarkers Prev* 2001, **10:**1287–1293.
118. Garner EI, Stokes EE, Berkowitz RS, *et al.*: **Polymorphisms of estrogen-metabolizing genes CYP 17 and catechol-o-methyltransferase and risk of epithelial ovarian cancer.** *Cancer Res* 2002, **62:**3058–3062.
119. Lurie G, Wilkens LR, Thompson PJ, *et al.*: **Genetic polymorphisms in the Paraoxonase I gene and risk of ovarian epithelial carcinoma.** *Cancer Epidemiol Biomarkers Prev* 2008, **17:**2070–2077.
120. Lurie G, Wilkens LR, Thompson PJ, *et al.*: **Genetic polymorphism in the estrogen receptor beta (ESR2) gene and the risk of epithelial ovarian carcinoma.** *Cancer Causes Control* 2009, **20:**47–55 Epub 2008 Aug 15.
121. Goodman MT, Laurie G, Thompson PJ, *et al.*: **Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk.** *Endocr Relat Cancer* 2008, **15:**1055–1060.