INTRODUCTION

Ovarian carcinoma is the fourth leading cause of cancer death in women and the most fatal gynecologic malignancy. Approximately 70 percent of patients with a diagnosis of ovarian carcinoma will present as Stage III or IV. Modern surgery and cytotoxic chemotherapy will produce a complete clinical response in 70 percent of patients. However, the majority of patients will experience relapse and the response to “salvage treatments” is often brief. These results are not surprising, as adjuvant therapy for most advanced-stage solid tumors rarely yields high durable response rates. Therefore, treatment of advanced ovarian carcinoma has yielded little improvement in long-term survival over the past 30 years.

Recognizing that therapeutic intervention of any advanced-stage solid tumor is unlikely to produce a substantial cure rate, attention has been given to screening to
identify early-stage disease amenable to curative resection. The fundamental challenge in this strategy centers upon the relatively low prevalence of this disease. As such, the effectiveness of any screening strategy will be severely hindered by a low-positive predictive value. Given an estimated prevalence of 50 cases per 100,000 population, a test with 99% specificity and 100% sensitivity would yield only one in 21 women undergoing surgical intervention with ovarian cancer. The screening trials performed to date would support these problematic statistics.

A representative study by Jacobs et al. utilized screening with CA-125 and ultrasound in 22,000 subjects. These authors identified 41 women with positive screening results, of whom 11 were noted to have cancer. It is important to note that 70 percent of the screening-identified cancers were Stage III or IV. Results such as these have led an NIH-consensus conference to conclude that “there is no evidence available yet that the current screening modalities of CA-125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer….” Even the most novel and, thus far, the most specific screening test for ovarian cancer is not specific enough for widespread application. Petricoin et al. recently reported on a proteomic approach to screening serum samples for protein expression patterns that might suggest ovarian cancer. The sensitivity of 100 percent and specificity of 95 percent is very promising for use in high-risk women. But, these test characteristics would lead to a positive predictive value that is too low for use in the general low-prevalence population.

Strategies that focus on prevention may, therefore, provide the most rational approach for meaningful reductions in deaths attributable to ovarian carcinoma. Increasing knowledge of inheritable genetic lesions in cohorts of patients allows for the identification of high-risk populations. Moreover, while many of the molecular events leading to the development of ovarian cancer are unknown, a carcinogenic pathway has been suggested that involves uninterrupted ovulation in a growth-stimulating hormonal milieu leading to increased probability of genetic lesions and expansion of tumorigenic clones.

HISTORICAL PERSPECTIVES AND OBSERVATIONS

Pregnancy is a physiological state associated with prolonged periods of anovulation and accompanied by high levels of circulating progesterone. Epidemiological studies have documented that multiparity is associated with decreased risk of ovarian cancer. Specifically, compared with nulligravidous women with a relative risk of 1.0, women with a single pregnancy have a relative risk of 0.6 to 0.8, with each additional pregnancy lowering risk by about 10 to 15 percent.

Several studies have also shown a reduced risk of ovarian cancer with the use of oral contraceptives (OCs) (Table 1). A reduction in risk is apparent after only a few months of use, but the apparent protection is greatest among long-term users. The reduction in risk for women who have used combination estrogen-progestin oral contraceptives for at least three years is approximately 40 percent. And the reduction in risk appears to persist for a number of years after discontinuation.

The proposition that environmental carcinogens may play a role in the development of ovarian carcinoma is supported by data on the increased risk associated with perineal use of talc, as well as the protective effect of surgical interventions that occlude the physiological pathway from the environment to the ovary. Observational studies have demonstrated a reduced risk of ovarian carcinoma following tubal ligation and hysterectomy even when the ovaries are left in situ.
Historically, theories regarding the pathogenesis of ovarian carcinoma have centered on the process of incessant ovulation. In theory, ovulation through the ovarian epithelium with subsequent repair occurs in a hormonal milieu conducive to induction and growth of a dysregulated clone. If a patent oviduct and uterus (not occluded by hysterectomy or tubal ligation) are present, potential carcinogens could gain entry, thus influencing the carcinogenic potential of early transformed cells. Incessant ovulation therefore increases the probability of mutational events that lead to propagation of an initiated cell; this may lead to additional events associated with the transformation to a clinically relevant cancer.

The proposed protective benefit of both pregnancy and the use of oral contraceptives has centered on reduction of ovulatory events leading to decreased probability of genetically-damaged cells. However, recent investigations have suggested that progestins may influence apoptosis leading to the demise of cells that are molecularly damaged and thus may become malignant.12,13

### CHEMOPREVENTION STRATEGIES

#### Oral Contraceptives

Oral contraceptives have been demonstrated repeatedly to reduce the subsequent risk of ovarian carcinoma in observational studies.

| Author                  | Date | Type of Study | Cases | Controls or Cohort Size | Odds Ratio or Relative Risk | 95% CI  |
|-------------------------|------|---------------|-------|-------------------------|----------------------------|--------|
| Ness et al.14           | 2001 | Case-control  | 727   | 1,360                   | 0.6                        | 0.5 – 0.8 |
| Siskind et al.15        | 2000 | Case-control  | 794   | 853                     | 0.57                       | 0.4 – 0.82 |
| Narod et al.16          | 1998 | Case-control  | 207   | 161                     | 0.5                        | 0.3 – 0.8 |
| Vessey and Painter17    | 1995 | Cohort        | 42    | 15,292                  | 0.3                        | 0.1 – 0.7 |
| Hankinson et al.18      | 1995 | Cohort        | 260   | 121,700                 | 0.65                       | 0.4 – 1.05 |
| Rosenberg et al.19      | 1994 | Case-control  | 441   | 2,065                   | 0.6                        | 0.4 – 0.8 |
| John et al.20           | 1993 | Case-control  | 110   | 246                     | 0.62                       | 0.24 – 1.6 |
| Parazzini et al.21      | 1991 | Case-control  | 505   | 1,375                   | 0.7                        | 0.5 – 1.0 |
| Franceschi et al.22     | 1991 | Case-control  | 971   | 2,258                   | 0.6                        | 0.4 – 0.8 |
| Parazzini et al.23      | 1991 | Case-control  | 91    | 237                     | 0.3                        | 0.2 – 0.6 |
| Gwinn et al.24          | 1990 | Case-control  | 436   | 3,833                   | 0.5                        | 0.5 – 0.7 |
| CASH Group25            | 1987 | Case-control  | 546   | 4,228                   | 0.6                        | 0.5 – 0.7 |
| Tzonou et al.26         | 1984 | Case-control  | 150   | 250                     | 0.4                        | 0.1 – 1.1 |
| La Vecchia et al.27     | 1984 | Case-control  | 209   | 418                     | 0.6                        | 0.3 – 1.0 |
| Rosenberg et al.29      | 1982 | Case-control  | 136   | 187                     | 0.6                        | 0.4 – 0.9 |
| Cramer et al.29         | 1982 | Case-control  | 144   | 139                     | 0.11                       | 0.04 – 0.33 |
| Willett et al.30        | 1981 | Case-control  | 47    | 464                     | 0.8                        | 0.4 – 1.5 |
| Weiss et al.31          | 1981 | Case-control  | 112   | 552                     | 0.57                       | Not stated |
Historically, the effect has been attributed to reduction in the number of ovulatory events associated with regular use of OCs. More recent data, however, suggest that the protective effect of OCs may be more complex. An innovative study that supports the use of progestins as chemopreventive agents in ovarian carcinoma was recently published by Rodriguez et al. In a randomized design, these authors examined the effect on ovarian epithelium of levonorgestrel in 130 ovulatory macaque monkeys. This progestin was administered over a period of 35 months at the end of which their ovarian epithelia were examined for apoptosis using immunohistochemical techniques. These authors demonstrated significantly-increased apoptotic cell counts in the ovarian epithelium of animals exposed to progesterone and hypothesized that progestin-induced apoptosis of the ovarian epithelium is responsible for the chemopreventive effect of OCs. This idea is a departure from the widely accepted theory that suppression of incessant ovulation is responsible for reduced risk of ovarian cancer. Moreover, they theorized that oral contraceptive progestins may decrease the risk of ovarian cancer by increasing the tendency of ovarian epithelial cells that have incurred genetic damage but are not yet neoplastic, to undergo apoptotic death.

Several studies have suggested that the degree of protection is associated with the duration of use of OCs. The length of protection also appears to be strongly correlated with duration of use. Prolonged risk reduction has been reported when OCs are used longer than four to six years, and minimal benefit has been observed if utilization is restricted to a period of six months to two years. Furthermore, the protective benefit of OCs diminishes with time and returns to baseline approximately 15 years after last regular use of OCs.

The influence of the estrogen/progestin content of a particular OC on subsequent ovarian cancer risk is an issue needing further study. Ness et al. demonstrated identical risk reduction for oral contraceptives with high-estrogen/high-progesterone content when compared with low-estrogen/low-progesterone content pills. However, a recent observational study by Schildkraut et al. suggested that low-progesterone OC formulations were associated with a significantly higher risk of ovarian cancer when compared with high-progesterone potency OC formulations.

One of the strongest risk factors for the subsequent development of ovarian cancer is a history of multiple affected family members. Studies by Gross et al. and Tavani et al. have demonstrated a risk reduction with OC use in women with strong family histories. These results have led Tavani et al. to suggest that five years of OC use in “high-risk women” can reduce ovarian cancer risk to the level observed in studies of low-risk women and in high-risk women who never used OCs but have parity as a protective factor. Further study is needed, however, in actual BRCA1 or BRCA2 gene mutation carriers, mutations with high risk of ovarian cancer. While an initial study by Narod et al. of 207 women with confirmed BRCA1/BRCA2 mutations demonstrated a statistically-significant risk reduction with OC use; this finding was not confirmed in a subsequent study of 244 women by Modan, where a risk reduction was present but not statistically significant. Thus, further studies of the association between OCs and ovarian cancer in women with BRCA1 and BRCA2 mutations are necessary to clarify this issue.

The protective effect of oral contraceptives would appear to be consistent across races as John et al. demonstrated a reduction in risk of 0.6 in African-American women with OC use of six years or more.
Non-steroidal Anti-inflammatory Drugs (NSAIDs) and Acetaminophen

NSAIDs have generated significant enthusiasm as chemopreventive agents, particularly for colon carcinoma. While some observational studies suggest a reduction of ovarian carcinoma risk with the use of some NSAIDs, the rationale for their use as chemopreventive agents has been lacking. However, recent animal studies examining the effects of NSAIDs on normal ovulation shed light on the potential mechanisms. Foremost, several classes of NSAIDs have been demonstrated to inhibit ovulation across multiple species of vertebrates. Indomethacin appears to inhibit ovulation in a dose-dependent fashion. In vitro analysis has suggested that inhibition of cyclooxygenase-2 (COX-2) leads to downregulation of local prostaglandins that may result in interactions with downstream mediators of surface epithelial cell apoptosis inhibiting rupture of the epithelial lining of the dominant follicle. NSAIDs have also been demonstrated to result in potent growth inhibition and increased apoptosis in ovarian cancer cell lines.

Interesting evidence for an antigonadotropic effect in animals also exists for acetaminophen. Acetaminophen has a phenol ring, similar to estradiol, and an acetyl group similar to progesterone, indicating a potential sex steroid-antagonist property. Evidence of antigonadotropic activity was suggested by toxicology studies demonstrating uterine, ovarian, and testicular atrophy in rats fed acetaminophen at 25,000 parts per million. In this study, the frequency of ovarian follicles was 23 percent in mice exposed to 3,000 to 6,000 parts per million acetaminophen compared with 38 percent of mice either not exposed or minimally exposed.

Several observational studies of the association between analgesic use and risk of ovarian cancer have yielded inconclusive results (Table 2). Compared with women who used aspirin rarely or not at all, Cramer et al. demonstrated a 25% reduction in risk among women with at least weekly use of aspirin over a six-month period, while Tavani et al. demonstrated a 28% lower risk in “former users” of aspirin. One should interpret these results with caution, however, as neither was statistically significant, and a study by Moysich demonstrated no evidence of reduced risk in aspirin users.

### Table 2

| Author          | Analgesic | Cases | Controls | Odds Ratio | 95% CI     |
|-----------------|-----------|-------|----------|------------|------------|
| Moysich et al.  | Aspirin   | 547   | 1,094    | 1.00       | 0.73 – 1.39|
|                 | Acetaminophen | 547   | 1,094    | 0.56       | 0.34 – 0.86|
| Tavani et al.   | Aspirin   | 749   | 898      | 0.93       | 0.53 – 1.62|
| Rosenberg et al.| NSAIDs    | 780   | 2,053    | 0.50       | 0.20 – 0.90|
|                 | Acetaminophen | 780   | 2,053    | 0.90       | 0.60 – 1.40|
| Cramer et al.   | Aspirin   | 563   | 523      | 0.75       | 0.52 – 1.10|
|                 | Ibuprofen | 563   | 523      | 1.03       | 0.64 – 1.64|
|                 | Acetaminophen | 563   | 523      | 0.52       | 0.31 – 0.86|

*All studies were case-control studies.*
Epidemiological evidence also exists for acetaminophen’s chemopreventive activity. Cramer et al. found that ovarian cancer risk among daily acetaminophen users was 61 percent lower than among nonusers. Similarly, Moysich et al. observed a 44% reduction in risk with regular acetaminophen use (defined as use at least once a week). In both studies, the protective effect of acetaminophen was statistically significant. Rodriguez et al. also reported a 45% lower death rate from ovarian cancer in women using acetaminophen daily; however, this finding was not statistically significant. In this particular study, only five percent or 5,731 women (out of 11,482 women reporting any acetaminophen use) reported daily acetaminophen use, and this small number of subjects could have contributed to a wider confidence interval. A case-control study reported by Rosenberg et al. examining the potential protective benefit of regular acetaminophen use found little evidence of an ovarian cancer risk reduction associated with this analgesic. However, taken together, current data presents a rational argument for the continued study of these agents in clinical and preclinical investigations.

Retinoids

An agent used for chemoprevention should have the capacity to cause cellular differentiation or lead to apoptosis in an initiated cell destined to become malignant. Experimental evidence indicates that retinoids can inhibit growth and promote cellular differentiation in ovarian cancer cells. In vitro experiments have demonstrated growth inhibition after application of all-trans retinoic acid to CAOV3 ovarian carcinoma cells. Additionally, Caliaro et al. and Brooks et al. have demonstrated increased induction of cytokeratins in cultures of ovarian cancer cells exposed to retinoic acid, suggesting a role in the differentiation of these cells. Finally, Supino et al. exposed A2780 ovarian cancer cell cultures to fenretinide and observed an increase in apoptosis.

The ability of retinoids to prevent ovarian carcinoma is also suggested in an interventional study in humans by Veronesi, De Palo, and colleagues. These authors reported a Phase III trial of fenretinide for the prevention of second breast cancers. Subgroup analysis demonstrated a significantly lower incidence of ovarian cancer in the treatment group. These results, however, must be interpreted with caution due to the limited number of ovarian cancer cases and the statistical pitfalls inherent in subgroup analyses. These studies have helped define the basis for an ongoing clinical trial (GOG190) examining the tissue effects of preoperative fenretinide administration over four to six months in women undergoing prophylactic oophorectomy due to high familial risk of ovarian cancer.

SURGICAL STRATEGIES

The ability to define populations of women at increased inherited risk for ovarian cancer has made prophylactic oophorectomy (BSO) in these women a rational consideration. Recent studies defining lifetime risk for ovarian cancer in women with BRCA1 mutations would suggest a cumulative risk of 15 to 30 percent. Additionally, increased risk of ovarian cancer is present with mismatch repair gene defects observed in the Lynch Type II syndrome. Vasen et al. have suggested an eight-fold elevation in risk of ovarian cancer in women with hereditary non-polyposis colorectal cancer. While it is tempting to recommend oral contraceptives or prophylactic surgical procedures to these patients, further study is needed in the context of this syndrome before recommendations for these preventive measures can be made.
A decision analysis has been performed to assess the effectiveness of prophylactic oophorectomy in women with BRCA1 mutations. Schrag et al. constructed two hypothetical populations of women: one consisting of women age 30 and the other consisting of women age 60, both with BRCA1 mutations, undergoing oophorectomy. A potential benefit of up to 1.7 years of life gained was observed in the modeled cohort of women age 30. In addition, it appeared that any benefit was minimal in women of age 60 and that a delay of BSO of up to ten years in the 30-year-old cohort did not decrease life expectancy.

When considering the risk of the procedure, a risk level appreciably lower than the risk of disease would be desirable. A study by Eltabbakh et al. examined 62 women undergoing BSO due to family history. Two operative complications were noted (intraoperative vascular complication and postoperative bleeding) and no deaths were reported. Therefore, in patients with elevated-inherited risk of ovarian carcinoma, it seems reasonable to consider prophylactic oophorectomy after child bearing is completed. Patients should also be aware of theoretical concerns regarding the unlikely survival benefit of undergoing prophylactic oophorectomy after age 60.

Patients undergoing prophylactic oophorectomy must be counseled that the reduction in risk of ovarian-type cancers is not absolute. Piver et al., in reviewing the Gilda Radner Familial Ovarian Cancer Registry, identified 324 women who had undergone prophylactic BSO. These authors identified six women (2 percent) who developed ovarian-type cancer either from a remnant segment of ovarian tissue or carcinoma of the peritoneal “field” one to 27 years after surgery.

A substantial number of women undergoing prophylactic oophorectomy will have an occult cancer of the ovaries identified on histological review. In the combined series of Salazar et al. and Deligdisch et al., three of 51 patients undergoing prophylactic oophorectomy were found to have occult-early ovarian cancers. In addition, a recent series published by Scheuer et al. identified one early-stage ovarian cancer and one early-stage fallopian tube cancer in 90 women undergoing prophylactic oophorectomy. Additionally, these authors reported that three additional cases of early-stage cancer were detected by preoperative screening in these high-risk individuals. A larger series is needed to confirm the true risk of occult cancer, however, as no early ovarian carcinomas were identified by Barakat et al. in 18 patients undergoing prophylactic oophorectomy. This finding underscores the need for adequate communication between the pathologist and surgeon, as well as careful histological examination using multiple sections of these ovarian specimens.

More recently, two prospective investigations have confirmed the effectiveness of risk-reducing surgery in patients carrying BRCA gene mutations. In the report by Kauff et al. one case of ovarian-type cancer was subsequently diagnosed in 98 women undergoing BSO, compared with four ovarian cancers identified in 72 women not undergoing surgery after a median follow-up of two years. A significant reduction in the hazard ratio for development of breast cancer was also observed.

Similarly, Rebbeck et al. also observed a protective benefit for subsequent development of both breast and ovarian cancer in BRCA mutation-positive individuals undergoing risk-reducing bilateral salpingoophorectomy. These authors compared 259 women undergoing BSO with 292 matched controls. Six women (2.3 percent) were diagnosed with Stage I ovarian cancer at the time of surgery. After a mean follow-up of 8.8 years, prophylactic oophorectomy significantly reduced the risk of developing ovarian cancer in these high-risk individuals (hazard ratio 0.04; 95 percent confidence interval 0.01 to 0.16).
This important study offers the strongest evidence to date of the potential benefit of risk-reducing prophylactic oophorectomy in high-risk individuals. While not recommended as a sole procedure for prophylaxis against the development of ovarian cancer, retrospective reviews have noted decreased risk of developing ovarian cancer among women who had undergone tubal ligation (Table 3). This interesting finding suggests that limiting exposure of the ovary to environmental carcinogens can help prevent ovarian cancer. The ability of tubal ligation to reduce the risk of ovarian cancer appears to be operative in individuals with BRCA1 or BRCA2 mutations. Narod et al. compared 232 BRCA-positive women with a history of ovarian cancer to 232 BRCA-positive control women. A history of tubal ligation was associated with a statistically significant 63% reduction in risk.

In spite of the protective effect of tubal ligation, it would seem prudent to remove the adjacent ovaries if laparoscopic surgery is contemplated in women at elevated risk due to genetic testing or strong family history of ovarian carcinoma.

CONCLUSIONS

Primary prevention of ovarian cancer may hold promise toward reducing deaths due to this insidious disease. However, it is very important to consider the available interventions in the context of a patient's overall health. Any surgery has risks as does administration of oral contraceptives. Moreover, these interventions must also be considered in the context of the patient's reproductive choices and desires.

To date, prevention of ovarian carcinoma represents an underdeveloped field of study. However, continued developments in molecular biology, biological therapeutics, and pathogenesis/carcinogenesis are creating a solid rationale to explore prevention as a rational approach to reducing deaths from ovarian carcinoma. As such, the rationale for prevention strategies is compelling enough to justify current clinical trials in the NCI-sponsored Gynecologic Oncology Group (GOG) and the Specialized Programs of Research Excellence (SPORES) in Ovarian Cancer.

Thus far, three clinical trials have been established at SPORE institutions that administer a chemopreventive agent followed by prophylactic oophorectomy to examine the

| Author                | Date | Type of Study | Cases | Controls or Cohort Size | Odds Ratio or Relative Risk | 95% CI |
|-----------------------|------|---------------|-------|-------------------------|----------------------------|--------|
| Ness et al.           | 2001 | Case-control  | 727   | 1,360                   | 0.50                       | 0.40 – 0.70 |
| Narod et al.          | 2001 | Case-control  | 232   | 232                     | 0.37                       | 0.21 – 0.63 |
| Miracle-McMahill et al | 1997 | Cohort        | 799   | 395,405                 | 0.64                       | 0.42 – 0.96 |
| Green et al.          | 1997 | Case-control  | 824   | 855                     | 0.61                       | 0.46 – 0.85 |
| Cornelison et al.     | 1997 | Case-control  | 300   | 606                     | 0.52                       | 0.31 – 0.85 |
| Rosenblatt et al.     | 1996 | Case-control  | 393   | 2,563                   | 0.72                       | 0.48 – 1.08 |
| Hankinson et al.      | 1993 | Cohort        | 156   | 121,700                 | 0.33                       | 0.16 – 0.64 |
potential tissue effects induced by these agents. The agents under study include COX-2 inhibitors at the University of Alabama at Birmingham, oral contraceptive formulations at the University of Texas MD Anderson Cancer Center, and retinoids at Fox Chase Cancer Center in conjunction with the GOG cooperative group mechanism.

It is our intention that by disseminating information regarding recent advances in the prevention of ovarian cancer, including chemoprevention, new investigative endeavors will be stimulated.

REFERENCES

1. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and etoposide compared with paclitaxel and etoposide in patients with stage III and stage IV ovarian cancer. N Engl J Med 1996;334:1-6.

2. Partridge EE, Barnes MN. Epithelial ovarian cancer: Prevention, diagnosis, and treatment. CA Cancer J Clin 1999;49:297-316.

3. NIH Consensus Development Panel on Ovarian Cancer. Ovarian cancer; screening, treatment and follow-up. JAMA 1998;279:491-497.

4. Jacobs I, Davies AP, Bridges J, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. BMJ 1993;306:1030-1034.

5. Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. Lancet 2002;359:572-577.

6. Engstrom P, Meykens FL. Cancer prevention. In: Hoskins W, Perez C, Young R, eds. Principles and Practice of Gynecologic Oncology. Philadelphia: Lippincott-Raven, 1997.

7. Hankinson SE, Colditz GA, Hunter DJ, et al. Risk factors for epithelial ovarian tumors of borderline malignancy. Int J Epidemiol 1991;20:871-877.

8. Longo DL, Young RC. Cosmetic talc and ovarian cancer. Lancet 1979;2:349-351.

9. Wong C, Hempling RE, Piver MS, et al. Peritoneal talc exposure and subsequent epithelial ovarian cancer: A case control study. Obstet Gynecol 1992;80:708-714.

10. Cornelison TL, Natarajan N, Piver MS, et al. Tubal ligation and the risk of ovarian carcinoma. Cancer Detect Prev 1997;21:2813-2818.

11. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. JAMA 1993;270:871-877.

12. Rodriguez GC, Walmer DK, Cline M, et al. Effect of progestin on the ovarian epithelium of macaques: Cancer prevention through apoptosis? J Soc Gynecol Invest 1998;5:271-276.

13. Risch HA. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 1998;90:1774-1786.

14. Ness RB, Grisso JA, Vergona R, et al. Oral contraceptives, other methods of contraception, and risk reduction for ovarian cancer. Epidermiology 2001;12:307-312.

15. Siskind V, Green A, Bain C, et al. Beyond ovulation: Oral contraceptives and epithelial ovarian cancer. Epidemiology 2000;11:106-110.

16. Narod SA, Risch H, Mosleh R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary ovarian cancer clinical study group. N Engl J Med 1998;339:424-428.

17. Vessey MP, Painter R. Endometrial and ovarian cancer and oral contraceptives—findings in a large cohort study. Br J Cancer 1995;71:1340-1342.

18. 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.

19. Rosenberg L, Palmer JR, Zauber AG, et al. Oral contraceptive use and the risk of epithelial ovarian cancer: A prospective study of reproductive factors and risk of epithelial ovarian cancer. Cancer 1995;76:284-290.

20. John EM, Whitemore AS, Harris R, et al. Characteristics relating to ovarian cancer risk: Collaborative analysis of seven US case control studies. Epithelial ovarian cancer in black women. Collaborative Ovarian Cancer Group. J Natl Cancer Inst 1993;85:142-147.

21. Parazzini F, La Vecchia C, Negri E, et al. Oral contraceptive use and the risk of ovarian cancer: An Italian case control study. Eur J Cancer 1991;27:594-598.

22. Franceschi S, Parazzini F, Negri, E, et al. Cooled analysis of 3 European case-control studies of epithelial ovarian cancer. II Oral contraception. Int J Cancer 1991;49:61-65.

23. Parazzini F, Restelli C, La Vecchia C, et al. Risk factors for epithelial ovarian tumors of borderline malignancy. Int J Epidemiol 1991;20:871-877.

24. Gwinn ML, Lee NC, Rhodes PH. Pregnancy, breast feeding, and oral contraceptives and the risk of epithelial ovarian cancer. J Clin Epidemiol 1990;43:559-568.

25. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. The reduction of risk of ovarian cancer associated with oral-contraceptive use. N Engl J Med 1987;316:650-655.

26. Tsouou A, Day NE, Trichopoulos D, et al. The epidemiology of ovarian cancer in Greece: A case-control study. Eur J Cancer Clin Oncol 1994;20:1045-1052.

27. La Vecchia C, Franceschi S, Decarli A. Oral contraceptive use and the risk of epithelial ovarian cancer. Br J Cancer 1994;70:31-34.

28. Rosenberg L, Shapiro S, Stone S, et al. Epithelial ovarian cancer and combination oral contraceptives. JAMA 1982;247:3210-3212.

29. Cramer DW, Hutchison GB, Welch WR. Factors affecting the association of oral contraceptives and ovarian cancer. N Engl J Med 1982;307:1047-1051.

30. Willett WC, BAIN C, Hennekens CH. Oral contraceptives and risk of ovarian cancer. Cancer 1981;48:1684-1687.

31. Weiss NS, Lyon JL, Lif J, et al. Incidence of ovarian cancer in relation to the use of oral contraceptives. Int J Cancer 1981;28:669-671.

32. Wu ML, Whitemore AS, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. J Reproductive and menstrual events and oral contraceptive use. Ann J Epidemiol 1988;128:1216-1227.

33. Gross TP, Schlesselman JJ, Stadel BV, et al. The risk of epithelial ovarian cancer in short-term users of oral contraceptives. Am J Epidemiol 1992;136:46-53.

34. Hartge P, Trowell PH, Paffenbarger RS Jr, et al. Rates and risks of ovarian cancer in subgroups of white women in the United States. The Collaborative Ovarian Cancer Group. Obstet Gynecol 1994;84:760-764.
35. Ness RB, Grasso JA, Klapper J, et al. Risk of ovarian cancer in relation to estrogen and prog- estin dose and use characteristics of oral contra- ceptives. SHARE Study Group. Steroid Hormones and Reproductions. Am J Epidemiol 2000;152:233-241.

36. Schildkraut JM, Calingaert B, Marchbanks PA, et al. Impact of progesterin and estrogen poten- cy in oral contraceptives on ovarian cancer risk. J Natl Cancer Inst 2002;94:32-38.

37. Tavani A, Racci E, La Vecchia C, et al. Influence of menstrual and reproductive factors on ovarian cancer risk in women with and without family history of breast or ovarian cancer. Obstet Gynecol 1994;83:419-424.

38. Ness RB, Grisso JA, Klapper J, et al. Risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345:235-240.

39. Ahnen DJ. Colon cancer prevention by NSAIDs: What is the mechanism of action? Eur J Surg Suppl 1998;582:111-114.

40. Murdoch WJ, Lund SA. Prostaglandin-inde- pendent anovulatory mechanism of indu- methacin action: Inhibition of tumor necrosis factor alpha-induced sheep ovarian cell apoptosis. Biol Reprod 1999;61:1655-1659.

41. Espey LL, Kohda H, Mori T, et al. Rat ovari- an progestin level and ovulation as indicators of the strength of non-steroidal anti-inflammatory drugs. Prostaglandins 1988;36:875-879.

42. Ando M, Koh S, Irahara M, et al. Non-steroidal anti-inflammatory drugs (NSAIDs) block the late, prostanoid-dependent/ceramide-independent component of ovarian IL1 action: Implications for the ovulatory process. Mol Cell Endocrinol 1999;157:21-30.

43. Rodriguez-Burford C, Barnes MN, Oechslinger DK, et al. Effects of non-steroidal anti-inflammatory agents (NSAIDS) on ovarian carcinoma cell lines: Preclinical evaluation of NSAIDs as chemopreventive agents. Clin Cancer Res 2002;8:202-209.

44. Cramer DW, Harlow BL, Titus-Ernstoff L, et al. Over-the-counter analgesics and risk of ovar- ian cancer. Lancet 1998;351:104-107.

45. National Toxicology Program. Toxicology and carcinogenesis studies of acetaminophen in F344/N rats and B6C3F1 mice. NTP Technical Report 394. Research Triangle Park, NC, 1993.

46. Tavani A, Ballus S, La Vecchia C, et al. Aspirin and ovarian cancer: An Italian case-control study. Ann Oncol 2000;11:1171-1173.

47. Mosey KB, Mettlin C, Piver MS, et al. Regular use of analgesic drugs and ovarian cancer risk. Cancer Epidemiol Biomarkers Prev 2001;10:903-906.

48. Rodriguez C, Henley SJ, Calle EE, et al. Paracetamol and risk of ovarian cancer mortality in a prospective study of women in the USA. Lancet 1998;352:1354-1355.

49. Tsukada Y, Jishi MF, Piver MS, et al. Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A report of the Gilda Radner Familial Ovarian Cancer Registry. Cancer 1993;71:2751-2755.

50. Nabid H, Godwin AK, Daly MB, et al. Microscopic benign and invasive malignant neo- plasms and a cancer-prone phenotype in prophylactic oophorectomies. J Natl Cancer Inst 1996;88:1810-1820.

51. Deligdisch L, Gil J, Kernher H, et al. Ovarian dysplasia in prophylactic oophorectomy speci- mens: Cytogenetic and morphometric correla- tions. Cancer 1999;86:1544-1550.

52. Scheuer L, Kauf N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA1 mutation car- riers. J Clin Oncol 2002;20:1260-1268.

53. Barakat RR, Federici MG, Saigo PE, et al. Absence of premalignant histologic, molecular, or cell biological alterations in prophylactic oophorectomy specimens from BRCA1 hetero-zygotes. Cancer 2000;89:383-390.

54. Kauf N, Satagopan J, Robson M, et al. Risk reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. N Engl J Med 2002;346:1609-1615.

55. Rebbeck T, Lynch H, Neuhausen S, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. N Engl J Med; 2002:1616-1622.

56. Narod SA, Sun P, Ghadirian P, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: A case-control study. Lancet 2001;355:1467-1470.

57. Miracle-McMahill HL, Calle EE, Kosinski AS, et al. Tubal ligation and fatal ovarian cancer in a larger prospective cohort study. Ann J Epidemiol 1997;145:349-357.

58. Green A, Purdie D, Bain C, et al. Tubal steril- isation, hysterectomy and decreased risk of ovar- ian cancer. Survey of Women’s Health Study Group. Int J Cancer 1997;71:948-951.

59. Rosenblatt KA, Thomas DB. Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Cancer Epidemiol Biomarkers Prev 1996;5:933-935.