A workshop on the epidemiology of ovarian cancer was held at the National Institutes of Health, Bethesda, Maryland, on September 30, 1991. The goals of the workshop were to address: (a) reproductive factors; (b) exogenous hormone use; (c) diet, life style, and health practices; (d) tumors of low malignant potential and nonepithelial germ cell ovarian tumors; (e) prospective studies; (f) determinants of genetic susceptibility; and (g) directions for future research in ovarian cancer.

Session 1: Reproductive Factors
Alice Whittemore (Stanford University School of Medicine, Stanford, CA) reported preliminary results of the analysis of combined data from 12 U.S. case-control studies on ovarian cancer (1). The objective was to assess the influence on ovarian cancer risk of events affecting ovulation, such as timing of menarche and menopause, timing and outcome of pregnancies, duration of breastfeeding, and duration of OC use. These data were examined in light of two currently prevailing hypotheses about ovarian cancer risk. The "ovulation" hypothesis was proposed by Fathalla in 1971 (2). It states that repeated minor trauma to the epithelial surface of the ovary, caused by incessant ovulation, is a major risk factor for ovarian cancer. The "gonadotropin" hypothesis (3), proposed by Stadel a few years later, suggests that exposure of the ovarian epithelium to high levels of circulating pituitary gonadotropins enhances ovarian cancer risk.

The combined data showed strong trends of decreasing ovarian cancer risk with increasing parity, duration of breastfeeding, and duration of OC use. Failed pregnancies (i.e., spontaneous abortion, ectopic pregnancy, and miscarriage) were also protective, but less so than full-term pregnancies. There was a weak trend of cancer risk with age at menarche, no clear trend with age at menopause, and a greater risk reduction associated with each incremental month of pregnancy than with each month of OC use. The trends of decreasing ovarian cancer risk with increasing parity and duration of OC use are consistent with both the ovulation and gonadotropin hypotheses.

A month of breastfeeding 6 or more months after delivery was found to be less protective than a month within the first 6 months of delivery. This supports the ovulation hypothesis because the longer a woman breast-feeds, the less effective lactation is in suppressing ovulation. The risk reduction associated with breast-feeding conflicts with the gonadotropin hypothesis: in lactating women, follicle-stimulating hormone levels remain elevated until the return of ovarian estrogenic function. The gonadotropin hypothesis predicts that breast-feeding would increase the risk of ovarian cancer.

The relationship between infertility and increased ovarian cancer risk was also evaluated. Among nulliparous women, ovarian cancer risk did not vary by marital status or gravidity. There was a weak association with duration of longest attempt at pregnancy, total duration of unprotected intercourse before pregnancy, or history of clinically diagnosed infertility not attributed to fertility problems of the male. The risk was elevated among women whose infertility was attributed to inadequate ovulation and among women who had used fertility drugs.

Epithelial tumors of low malignant potential, frequently called borderline tumors, have various features of malignant epithelial ovarian cancers, but they do not invade the ovarian stroma. Women with these tumors are usually younger when diagnosed and have a better prognosis than women with malignant tumors. Oral contraceptives are generally less protective against borderline tumors than against malignant invasive tumors.

David Rose (American Health Foundation, Valhalla, NY) indicated that two widely discussed hypotheses of ovarian cancer causation (2, 3) may relate to dietary effects on endogenous hormones. Both hypotheses are compatible with the known international and regional associations between ovarian cancer risk and dietary fat consumption. Although such associations do not imply causality, the increase in incidence of ovarian, breast, and prostate cancers as fat consumption has increased in Japan is particularly striking.

The plasma estradiol and estrone levels of both premenopausal and postmenopausal women were found to decrease when they were switched from a typical high-fat (35–40% total calories from fat) diet to one providing only 20% or less of calories from fat. Switching from a low-fiber to a high-fiber diet had a similar effect. A low-fat diet also caused some reduction in midluteal phase plasma LH levels.

Rose stated that there are several studies of which epidemiologists should be particularly aware when thinking about ovarian cancer. For example, a study published by Lloyd et al. (4) merits confirmation and elaboration. This was a case-control study to examine the effect of nutritional factors on menstrual function and bone density in collegiate women. Three groups, matched with...
respect to age, height, and weight were studied: seden-
tary women with regular menses, athletic women with
regular cycles, and a small group of athletic women who
had become oligomenorrheic. Average age at menarche
was greater in normal (13.1 years) and oligomenorrheic
(14.3 years) athletes compared with the sedentary
women (12.2 years). Average bone density was lower in
the oligomenorrheic athletes compared with normal ath-
letes and sedentary women. Dietary fiber intake was
significantly higher in the oligomenorrheic women com-
pared with the other two groups of women. It was
concluded that increased dietary fiber intake was asso-
ciated with menstrual dysfunction in collegiate athletes.
Plasma hormones were not measured in this study. In
another study (5), menstrual irregularities were reported
among vegetarian women compared to omnivorous
women whose diets were somewhat higher in fat but
much lower in fiber. The significance of these findings in
the context of ovarian cancer risk needs further
consideration.

Pirke et al. (6) studied groups of premenopausal
women who were placed on weight-reducing diets, one
group receiving a vegetarian diet and the other a mixed
diet. Weight losses were similar in both groups, but after
6 weeks the women eating vegetarian diets exhibited a
shortening of the menstrual cycle and some became
anovulatory. These changes were associated with a sig-
ificant reduction in the height of the ovulatory plasma
LH peak and in the luteal phase LH concentrations.
Midluteal plasma estradiol levels were also reduced in
women on vegetarian diets.

Hill et al. (7) carried out a dietary intervention study
on 4 volunteer nurses. Two women who were switched
from a mixed diet to a vegetarian diet reported shortening
of the menstrual cycle by 1–2 days, and their serum LH
peak occurred earlier in the menstrual cycle and was of
reduced amplitude.

From these data, it seems that fat and fiber influence
the menstrual cycle, the hypothalamopituitary regulation
of ovulation, and the levels of circulating estrogens.
Moreover, it appears that a low fat/high fiber diet may
result in fewer ovulatory cycles, which could favorably
influence ovarian cancer risk.

PGs of the E and F series accumulate rapidly in the
preovulatory follicular fluid and reach a peak at ovulation,
the stimulus being provided by gonadotropins. Both LH
and estradiol accelerate PG production, with PGE con-
tributing to vasodilation and progesterone production,
and PGEs stimulating contraction of the myoid cells
involved in the extrusion of the oocyte follicle. Inhibition
of PG synthesis prevents rupture of the follicles, and suppres-
sion of ovulation can be induced in women by
treatment with a PG synthesis inhibitor, indomethacin. It
is not yet known whether long-term treatment with drugs
such as indomethacin reduces ovarian cancer risk.

Session 2: Exogenous Hormones
Malcolm Pike (University of Southern California, Los An-
geles, CA) began his presentation by pointing out that
the age-specific incidence of most non-hormone-de-
pendent epithelial cancers shows a linear increase (on a
log-log plot). However, there is a distinct reduction in
the rate of increase around age 50 (8). This protective
effect of menopause is the most fundamental epidemi-
ological fact about ovarian cancer. Since gonadotropin
levels are high in postmenopausal women, it seems that
high levels of gonadotropins per se may not be important
in the etiology of later-onset ovarian cancer. High levels
of gonadotropins may be important in premenopausal
women, however, when they have a “substrate” to work
on, namely oocytes.

Pregnancies have a greater protective effect (ex-
pressed as reduction in risk per month) than breast-
feeding or OC use, but the latter two variables are subject
to much greater measurement error. Three aspects of the
protective effects of OC use need further research. First,
how does this effect change with time and with increas-
ing age since stopping use? The Cancer and Steroid
Hormone Study data, for example, stop at age 54. Sec-
ond, Whittemore’s metaanalysis suggests that the use of
OCs for longer than 6 years confers no additional protec-
tion. This is contrary to other data (9, 10), and further
information on long-term use is needed either to refute
this finding or to try to explain it in terms of, for example,
the time to return of ovulation after cessation of OC use.
Third, do modern low-dose pills have the same protec-
tive effect on ovarian cancer risk as older higher-dose
pills? The answers to these questions are very important,
since they have a profound effect on the risk-benefit
equation for OC use.

The apparent lack of effect of age at menopause on
ovarian cancer risk described by Whittemore and col-
leagues is likely to shed light on the etiology of ovarian
cancer. Women who have had their last menstrual period
after age 53 have undoubtedly ovulated more times than
women whose last menstrual period was before age 45.
This observation may be evidence against the “incessant
ovulation” hypothesis.

Pregnancy, variables related to menstruation, and
OC use cannot explain the international differences in
ovarian cancer rates. It is conceivable that diet may
explain part of the geographic variation in ovarian cancer
rates.

Noel Weiss (University of Washington, Seattle, WA)
reported that although estrogens used for hormone re-
placement therapy may reduce gonadotropins to a level
between pre- and postmenopausal values, and hence
perhaps reduce risk of ovarian cancer, no evidence is
available to support a decreased risk of ovarian cancer
associated with the use of postmenopausal hormones.
Whittemore and colleagues have evaluated the relation-
ship of menopausal estrogens to the risk of epithelial
ovarian cancer using data from five hospital-based and
five population-based case-control studies.3 No clear
trends in risk were observed with increasing duration of
estrogen use or with increasing time since last estrogen
use after adjustment for duration of use. Overall, meno-
pausal estrogen use was unrelated to risk for epithelial
ovarian cancers of the endometrioid cell type. Weiss
observed a slightly increased risk in his study of meno-
pausal estrogen use and ovarian cancer risk (11).

Carlo La Vecchia (Istituto di Ricerche Farmacolo-
giche, Mario Negri, Milan, Italy) reported results of the
metaanalysis of three hospital-based case-control studies

A. S. Whittemore et al. Characteristics relating to ovarian cancer risk.
Malignant epithelial cancers versus menopausal estrogen use, submitted
for publication.
of ovarian cancer conducted in Greece, Italy, and the United Kingdom (12–14). In assessment of the roles of parity and age at first birth in parous women, both factors had a weak, nonsignificant influence on cancer risk. When parity and age at first birth were considered separately, there was an inverse trend in risk with increasing number of births. However, a significant trend emerged only from the British study and was largely restricted to women who reported four or more births. Compared to women who bore their first child at age 24 or less, the increase in risk for those who bore their first child at age 35 or more (RR 1.4) was of borderline statistical significance. The pooled analysis also indicated that abortions confer limited protection of 30–40% against ovarian cancer in women who reported two or more spontaneous or induced abortions.

Unlike the Whittomore analysis, there was no evidence of an association between ovarian cancer and age at menarche, and there was a consistent trend of increased risk with late age at menopause. The strength of the association was relatively weak, with a relative risk of less than 2 with menopause after age 52 compared with earlier menopause. The effect of age at menopause seemed to be long-lasting and to increase with age at diagnosis of ovarian cancer.

Compared with never-users, the RR for OC users was 0.6. The RR estimates for use of OCs were even lower in women reporting their first use before age 25. The risk of disease decreased with the duration of use, being 0.7 in women reporting OC use for less than 2 years and 0.4 for OC use for 5 years or more. The protection persisted even after discontinuing OC use, the RR being 0.5 in women reporting their last OC use 15 years or more before diagnosis of ovarian cancer. The protective effect of OC use on ovarian cancer emerged consistently in all age and parity strata.

Session 3: Diet, Life Style, and Health Practices
James Marshall (State University of New York, Buffalo, NY) reported on preliminary findings from an ongoing case-control study of diet and ovarian cancer. There was a slight excess of caloric intake among cases relative to controls. Crude dietary fiber appeared to exert some protective effect. Total vitamin A intake had a marginally significant protective effect, which seems to be due to β-carotene, not retinol. There was no relationship between obesity or alcohol intake and ovarian cancer.

Daniel Cramer (Brigham and Women's Hospital, Boston, MA) pointed out that the “incessant ovulation” hypothesis for the etiology of ovarian cancer does not have supporting animal models and does not fully explain risk factors such as early menopause, radiation, infertility, and heredity, or the protective role of pregnancy and oral contraceptive use. In 1948, Gardner (15) proposed that ovarian cancer was caused by hypergonadotropic hypogonadism, i.e., high secretion of gonadotropins due to ovarian failure or lack of feedback control on the pituitary. The theory was based on animal experiments, which demonstrated that if you caused oocyte death by gonadal irradiation or use of oocyte toxins such as polycyclic hydrocarbons, thereby raising gonadotropin levels, ovarian cancer resulted. Congenital deficiency of oocytes (germ cells) also increased ovarian cancer risk. That gonadotropin stimulation was a necessary component was inferred from the ability of pituitary ablation or deficiency of gonadotropin releasing hormone to block tumor development. Relevance of animal models to human disease models has been questioned, since animal tumors are primarily stromal, whereas human tumors are primarily epithelial. Cramer and Welch (16), however, proposed that a stimulus that causes stromal tumors in rodents may also promote different types of ovarian tumors in women. According to their theory, the first stage of tumorigenesis involves formation of inclusion cysts (islands of ovarian surface mesothelium) by entrapment of ovarian surface epithelium into the ovarian stroma. In the second stage, differentiation, proliferation, and eventual malignant transformation of the epithelium lining the inclusion cysts occur due either to direct stimulation by gonadotropins or to indirect stimulation by steroids induced by gonadotropins. In addition, Cramer et al. (17) speculate that talc may ascend the genital tract and become incorporated into the inclusion cysts, contributing to the risk of ovarian cancer, which is consistent with some epidemiological data.

Experimental and clinical studies have reported an association of galactose consumption and metabolism with hypergonadotropic hypogonadism. In a case-control study of ovarian cancer, Cramer et al. (18) found that women with ovarian cancer consumed dairy products with a higher content of prehydrolyzed lactose (yogurt and cottage cheese) and had lower concentrations of galactose-1-phosphate uridyltransferase, an enzyme that converts galactose to glucose, than did control women. Risk for ovarian cancer was related to the ratio of lactose consumption to transferase activity. Cases had a mean lactose consumption:transferase activity ratio of 1.17 compared with 0.98 for controls. There was a highly significant trend for increasing ovarian cancer risk with increasing lactose consumption:transferase activity ratio.

Biological specimens are needed to further investigate the possible interactions of various exposures with biochemical or molecular genetic factors, such as transferase activity. Cramer recommended expansion of familial ovarian cancer clinics, which will permit the identification and formation of pedigrees for linkage analysis, identification of phenotypic markers for ovarian cancer, collection of biological specimens, and identification of markers that precede tumor development. Such clinics encourage development of clinical strategies for primary and secondary disease prevention.

Mitsuru Mori (Kurume University, Kurume City, Japan) reported the results of two metaanalyses of published case-control studies on ovarian cancer. Tubal sterilization was found to be significantly associated with reduced risk of ovarian cancer when nulliparous women were excluded from the analysis. Since subfertility is related to both an increased risk of ovarian cancer and a decreased frequency of tubal sterilization the observed relationship could be indirect. Among Asian women, induced abortion had a slight protective effect.

It has been hypothesized that a potential carcinogenic agent enters the peritoneal cavity through the fallopian tube, irritates the pelvic peritoneum, produces proliferation, and, with additional factors, results in the development of cancer. If this hypothesis is correct, ligature of the fallopian tube may protect against ovarian cancer by preventing the cancer-promoting or -promoting agents from entering the peritoneal cavity.
Session 4: Borderline and Nonepithelial Tumors
Lawrence McGowan (George Washington University, Washington, DC) emphasized the need for obtaining a more detailed clinical history, greater involvement of a gynecologic pathologist, and closer interaction of a pathologist with an operating surgeon in studies of ovarian cancer. He stated that primary peritoneal carcinoma exhibits many symptoms similar to those of primary epithelial ovarian cancer and that therefore there is a possibility of misdiagnosis.

Currently, gynecological pathologists prefer the term "low malignant potential tumor" over "borderline tumor." Women with low malignant potential tumors are usually younger when diagnosed and have a better prognosis than women with malignant tumors. Analysis of combined data from nine case-control studies of ovarian cancer in the United States revealed that the risk profile for tumors of low malignant potential was similar to that for malignant ovarian tumors with two exceptions. The risk for low malignant potential tumors was less clearly reduced among women who had used OCs. There was clearly an elevated risk of low malignant potential tumors among women with a history of infertility. This was the greatest difference in risk factors between low malignant potential tumors and invasive carcinoma.

Carolyn Westhoff (Columbia University, New York, NY) stated that ovarian tumors of low malignant potential are almost entirely serous and mucinous epithelial tumors. When diagnosed, they tend to be localized to the ovary, which accounts for their good prognosis. There are very few data regarding their incidence. Frequent misclassification of these tumors reduces the value of data from clinical series.

Benign ovarian neoplasms can be of epithelial, stromal, or germ cell origin. Their occurrence is not recorded by tumor registries, and misclassification of the histological diagnosis is relatively common. The tumors of germ cell origin, the teratomas, are most common and have a unimodal age distribution with a peak near age 30; the shape of this age-incidence curve resembles that of testicular tumors. The benign epithelial tumors occur somewhat less frequently than teratomas, are more subject to diagnostic misclassification, and occur about equally among women from their teens through the 70s. No study has found any evidence that OCs protect against either the teratomas or the benign epithelial tumors; nulliparity and infertility may increase the risk of these tumors. The stromal tumors are rare and occur in postmenopausal women. There have not been any reported epidemiological studies of the stromal tumors.

Session 5: Prospective Studies
Graham Colditz (Channing Laboratory, Boston, MA) reported preliminary findings from an ongoing prospective study of over 121,000 registered U.S. nurses who were aged 30 to 55 when recruited in 1976. The original aim of the study was to look at exogenous and endogenous hormones and the risk of breast, uterine, and ovarian cancers. The questionnaire obtained details on the following reproductive factors: age at menarche; age at first birth; parity; weight and height; menopause, including type of menopause; if postmenopausal, use of replacement hormones; OC use, including details of interval of use, but not details of actual preparation used. Data were collected on different types of contraception, including tubal ligation and vasectomy. The cohort was followed with a biennial questionnaire, which allowed the women to update their exposure information.

Two hundred forty-seven ovarian cancers were reported in the nurses' cohort by the end of 1988. There was an inverse association, adjusted for parity, with the use of OCs. Women with five or more years of OC use had a relative risk of 0.6 for ovarian cancer. There was a decreasing risk with increasing parity. There was no clear relationship of risk with age at first birth, even after adjustment for parity. Long duration of postmenopausal hormone use appeared to increase risk slightly. The relative risk associated with tubal ligation, adjusted for age and parity, was 0.37.

A food frequency questionnaire was administered to the cohort in 1980. There was no suggestion of increasing risk with increasing saturated fat intake among the cases diagnosed during 8 years of follow-up. For lactose intake, only the top quintile had a slight excess of cases. To date, there is no relationship with alcohol intake, cigarette smoking, or various other nutrients examined.

Session 6: Family History and Genetic Events
Bruce Ponder (University of Cambridge, Cambridge, England) reviewed preliminary data from a large population-based study carried out using public health records in the United Kingdom. Information on cancer mortality by site in first-degree relatives (2106 parents and 1949 siblings) of 1183 index cases diagnosed with ovarian cancer before age 60 (who were under age 17 in 1939) was obtained. There was a substantially increased relative risk of death from ovarian cancer in first-degree relatives of cases. The risk appeared to be greatest when the index case was diagnosed before age 50. Despite the substantial relative risks, the absolute risks are still small, with a 1 in 40 chance of death from ovarian cancer by age 70 in a sister or mother of an index case diagnosed below age 50. However, there was heterogeneity in the data; women with two affected relatives were at very substantial risk. In these families, segregation analysis was consistent with the inheritance of a single autosomal dominant gene with high penetrance. This hypothesis can only be proved by demonstration of linkage between ovarian cancer and a known genetic marker, which appears to be a marker on the long arm of chromosome 17.

Ponder suggested the establishment of registries of women with ovarian cancers at different ages, sibling pairs, and pairs of closely related women with ovarian and breast cancer, so that studies can be initiated to determine the risk attributable to specific mutations. These families will be useful for pathology studies, since so little is known about the early stages of ovarian cancer development. There is a need for studies to assess the protective effect of prophylactic oophorectomy for women at high risk for ovarian cancer. Ponder concluded his remarks by briefly describing a U.K. National Study recently initiated to identify all families with two or more ovarian cancers.
Henry Lynch (Creighton University, Omaha, NE) emphasized the need for the establishment of familial cancer registries and the collection of information on cancer of all anatomic sites among family members. He also recommended the establishment of specimen banks to store rapidly frozen tumor, normal ovarian tissue, and DNA for distribution to interested investigators.

Session 7: Research Directions
David Schottenfeld (University of Michigan, Ann Arbor, MI) summarized three key areas for future research on ovarian cancer:

1. Family registry resources should be further developed to address linkage markers of susceptibility, assess the interactions of inherited risk with environmental exposures, and assess the value of possibly protective interventions such as the use of combination OCs or other chemopreventive agents.

2. Epidemiological studies should further address the relationship of variations in reproductive patterns to ovarian cancer, the potential risks associated with endogenous gonadotropin levels, and the use of exogenous hormones, such as estrogen hormone replacement therapy and fertility-promoting agents.

3. Studies of ovarian cancer should use precise pathologic classification.

References
Epidemiology of ovarian cancer.

A R Patel and G I Obrams