

Ovarian Cancer

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I. Introduction

Ovarian cancer poses a significant threat to women's health, especially in the western hemisphere. A white woman in the United States has a 2% chance of developing ovarian cancer and a 1% chance of dying from it [1]. Some patterns of risk for ovarian cancer parallel those for breast and endometrial cancer, but many do not. Existing theories for the development of ovarian cancer include epithelial trauma from repeated ovulations, exposure to elevated gonadotropin levels, and exposure to exogenous carcinogenic agents that enter the peritoneal cavity via the vagina. Extensive investigation of the epidemiology of this disease has provided a consistent picture of the major risk factors but has not yet revealed the fundamental etiology. Examination of the genetics, cytology, and pathology of ovarian cancer has shed light on the natural history but has not yet illuminated the sequence of changes from earliest genetic abnormality to overt disease. Detection of some early lesions by ultrasound or by serum assays has raised the prospect of screening but has not yet been established as effective in experimental trials. At this writing, the investigation of ovarian cancer proceeds on many fronts. Investigators hope for a convergence of findings in the near future that will substantially advance our understanding of this feared disease.

II. Biology of Ovarian Cancer

The ovaries are almond-sized organs covered with a thin layer of coelomic epithelium. Cancers may arise in any of the three basic cell types of the ovary: the surface epithelium, the germ cells, and the stroma [2]. Germ cell tumors are rare, occur at young ages, and include dysgerminomas, teratomas, and choriocarcinomas. About 90% of ovarian cancers are epithelial, and are further characterized as serous, endometrioid, or mucinous. Some evidence of etiologic heterogeneity among the epithelial cancer cell types has been presented, but the differences are uncertain and the epithelial cancers typically are grouped together in epidemiologic investigation. Similarly, borderline tumors, or cancers of low malignant potential, exhibit distinct clinical behavior but not distinct etiology and are generally included with invasive disease.

After menarche, each ovary typically ovulates on alternating months. With ovulation, follicular and luteal cysts occur commonly and appear not to affect risk of carcinoma. Microscopic inclusion cysts have been suggested to give rise to cancer but the evidence is conflicting [3].

At menopause, ovarian function ceases and the organs decrease in size. The age-specific risk of ovarian cancer parallels, but lags behind, the age-specific measures of normal ovarian function. Women with ovarian cancer typically come to diagnosis with nonspecific symptoms such as constipation, urinary frequency, or pelvic pressure [4]. Transvaginal [5] and abdominal ultrasound and serum level of the cancer antigen CA 125 [6] are among the tests used to make a diagnosis. By extension, these techniques are being evaluated as screening methods for early asymptomatic ovarian cancer.

III. Ovarian Cancer in Populations

A. Age-Specific Incidence and Mortality in U.S. Black and White Women

The age-adjusted incidence of ovarian cancer is 15 cases per 100,000 woman-years in the United States [1]. Incidence rates are low before the age of 40, increase exponentially until age 65, and plateau thereafter (Fig. 71.1). The age-adjusted incidence rates are 10.2/100,000 for women younger than 65 years of age and 57.9/100,000 for women 65 years of age and older. Mortality rates follow a similar pattern. The age-adjusted mortality rates are 7.8/100,000 for all ages, 3.9/100,000 for women younger than 65 years of age, and 43.6/100,000 for women 65 years of age and older. The overall five-year survival rate is 46.4% but is highly dependent on age and stage. Five-year survival rates are higher among younger women (78.1% for women <45 years of age vs 23.5% for women 75+), and for localized (92.6%) compared with distant (25.3%) disease. Most disease (57%), however, is diagnosed as distant rather than localized (24%) or regional (13%) stage. The stage distribution also depends on age, with younger women more likely to be diagnosed with earlier stage and older women with later stage disease.

Black women in the United States face somewhat lower risks of developing or dying from ovarian cancer (Fig. 71.1). The lifetime risk of being diagnosed with ovarian cancer is 1.86% among whites and only 1.15% among blacks, and risk of dying from ovarian cancer is 1.21% and 0.74%, respectively. The age-adjusted incidence rate in blacks is 10.9/100,000 compared with 15.6/100,000 in whites, and age-adjusted mortality rates are 6.6/100,000 and 8.0/100,000, respectively. Survival is similar in black and white women younger than 50 years of age but is slightly worse in older black women than in older white women (27.6% vs 36.6%). The stage distribution at diagnosis is similar for whites and blacks.

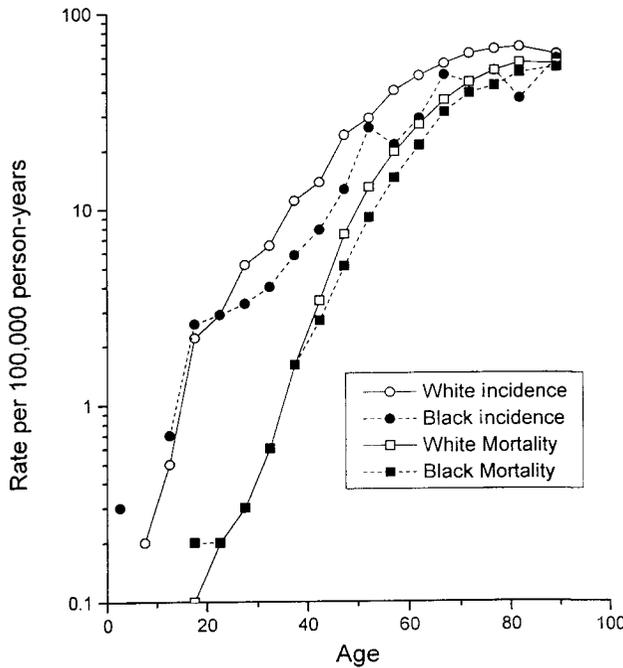


Fig. 71.1 Age-specific ovarian cancer incidence and mortality rates in U.S. black and white women, 1990-1994.

B. International Variation

Ovarian cancer develops two to three times more often in northern European women than in Japanese women, as shown

in Figure 71.2. Incidence rates are highest in the northern European countries, U.S. whites, Canada, Israel and New Zealand's non-Maori population. Rates in the Far East, the Caribbean, and Central and South America rank lowest. Such variation suggests lifestyle effects, but these effects are less marked than those for breast cancer.

C. Time Trends in Age-Specific Incidence and Mortality

Figure 71.3 presents time trends in the U.S. age-adjusted ovarian cancer mortality rates by race. Overall, mortality rates have decreased slightly since the late 1960s. White mortality rates have been consistently higher than nonwhite rates for decades. Mortality rates converged slightly in the 1950s with rates among nonwhites approaching those of whites. Since the 1950s, time trends by race have appeared to be similar, although an increase among blacks in recent years is suggested.

IV. Influences on Individual Risk

A. Genetics and Host Influences

Inherited ovarian cancers may account for 3-5% of all cases, with a larger fraction among the younger cases. Case-control studies suggest a three- or fourfold risk of ovarian cancer in women who have a first-degree relative diagnosed with ovarian cancer [7]. In families with multiple ovarian cancers, breast cancers also occur more often than expected. In addition, primary ovarian cancer develops more often than expected in women who have survived breast cancer [8].

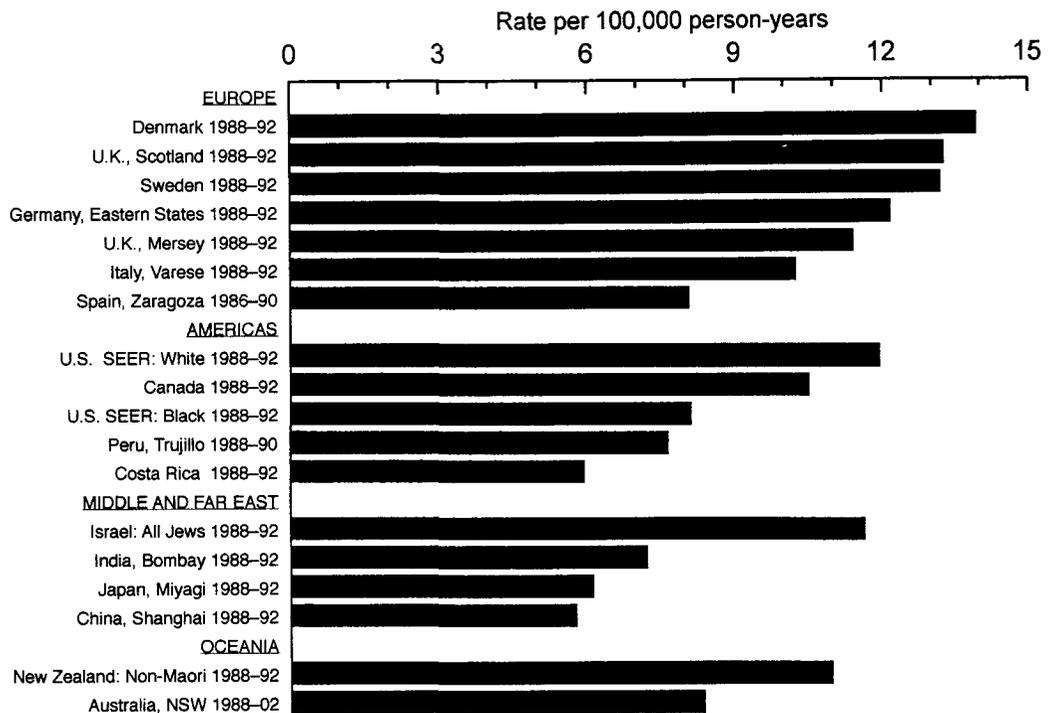


Fig. 71.2 International variation in ovarian cancer incidence rates by continent.

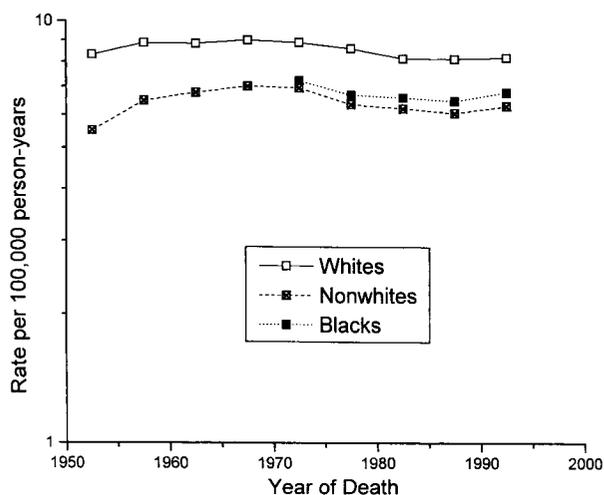


Fig. 71.3 Age-adjusted ovarian cancer mortality rates in the U.S., by race, 1950–1954 to 1990–1994.

In a fraction of families with unusual numbers of breast and ovarian cancers, perhaps 50%, it is possible to detect a mutation in BRCA1 [9] or BRCA2 [10]. Among women who carry a mutation in either of the genes, the risk of developing ovarian cancer is estimated to be 17% [11]. The proportion of disease associated with BRCA1 or BRCA2 is greater at younger ages, much as other genetically related cancers are most evident at younger ages. Some preliminary investigations suggest that the relative effect of a mutation on breast versus ovarian cancer may vary between BRCA1 and BRCA2 or vary depending on the locus of the mutation, but no firm conclusions can yet be drawn.

B. Reproductive Factors

Table 71.1 describes selected case-control and cohort studies of ovarian cancer and Table 71.2 summarizes the literature on the associations of the major reproductive factors with ovarian cancer risk. Several reproductive factors have been firmly associated with a reduced risk of ovarian cancer. Women who have had a full-term pregnancy have a lower risk of ovarian cancer than nulliparous women, and each subsequent birth confers additional protection [7]. In the analysis of combined U.S. case-control studies [7], risk of ovarian cancer was reduced by 13–19% with each live birth. The effect of pregnancy to reduce risk of ovarian cancer is independent of age at which a woman's first pregnancy occurs [7]. Incomplete pregnancies, due to spontaneous or induced abortion, may also decrease risk, although the protection afforded appears to be less than that associated with full-term pregnancies [7]. Another factor associated with a lower risk of ovarian cancer is oral contraceptive pill use. In virtually all studies, women who have used oral contraceptive pills are at lower risk of ovarian cancer than women who have not used them, and risk decreases by approximately 10% for every year of use [38]. Parous and nulliparous women probably experience similar protection from oral contraceptives [38,39] and are protected for at least 10 years after cessation of use [38]. Several types of gynecologic surgery also decrease risk of ovar-

ian cancer. Women who have had a tubal ligation [7,40–43] or hysterectomy (with preservation of at least one ovary) [7,15,40–43] have a lower risk of ovarian cancer, and the reduction in risk remains up to 15 years or more after surgery [41,43].

Other reproductive factors either do not appear to be related to ovarian cancer risk or are inconclusive. Most studies indicate that risk of ovarian cancer, unlike breast cancer, does not increase with an early age at menarche [7,23] or a late age at first birth [7,23]. Regularity of menstrual cycles does not appear to affect risk [18,19,26], and, though less studied, risk does not seem to vary by cycle length [18], amenorrhea [18], or premenstrual symptoms (*e.g.*, irritability, breast tenderness, edema) [19]. Women who have breastfed are at lower risk of ovarian cancer in studies conducted in the U.S. [7] and Australia [31], but most studies in other low-risk countries show no association with breastfeeding [17,19,30].

A relationship of infertility with ovarian cancer risk seems likely but has not been firmly established or clearly explained. Risk has been shown to increase with increasing number of contraceptive-free years of marriage [7,47] and is slightly elevated among nulligravida, but not gravid women who have a physician's diagnosis of infertility [7]. In the analysis of the combined U.S. case-control studies [7], risk was elevated among infertile women reporting ovulatory abnormalities, but not among women with other or unspecified types of infertility, compared with women reporting no history of infertility. The elevated risk, however, was restricted to women with a history of infertility who used fertility drugs. Studies of cancer risk in populations of infertile women [32,34,35,48] have generally had better information than case-control studies on type of infertility but have lacked sufficient numbers of ovarian cancer cases to assess risk. In a U.S. study of infertile women [35], no overall increase in ovarian cancer risk was observed, although an increase in risk was suggested for women with progesterone deficiency/oligoovulation/anovulation compared with other causes of infertility. In studies conducted in Israel [34,37], no overall association was found with infertility, but infertile women with adequate estrogen and progesterone production had a higher than expected frequency of ovarian cancer compared with population rates. In an Australian cohort of women referred for in-vitro fertilization (IVF) [33], risk associated with unexplained infertility was nearly twenty times that of infertility due to known causes after taking into account whether women were treated with fertility drugs. The results, however, were based on a small number of cases. Thus, it is possible that only certain types of infertility are associated with an excess risk of ovarian cancer.

Even if higher risk among infertile women is likely, the relationship of fertility drugs and ovarian cancer risk is inconclusive at present. Combined data from three U.S. case-control studies with information on fertility drug use revealed an increased risk of ovarian cancer among the infertile women who had used fertility drugs [7]. While risk of ovarian cancer was similar among fertile and infertile women, infertile women who had used fertility drugs had three times the risk of women lacking a history of infertility. Most of the increase in risk associated with fertility drug use was observed among infertile women who remained nulligravid. In a cohort study of U.S. infertile women [32], prolonged use of clomiphene citrate, a common fertility drug, was associated with 11 times the risk of ovarian cancer

Table 71.1
Selected Epidemiologic Studies of Ovarian Cancer

Geographic area	Years	Subjects	Age
Case-control studies^a			
London and Oxford, U.K. [12]	1978–1983	235/451 (hospital)	<65
Milan, Italy [13,14]	1983–1987	634/1,626 (hospital)	22–74
	1979–1980	161/561 (hospital)	19–69
Athens, Greece [15,16]	1989–1991	189/200 (hospital visitors)	<75
	1980–1981	150/250 (hospital)	all
Hokkaido, Japan [17]	1980–1981	110/220 (hospital, outpatient)	all
	1985–1986		
Shanghai, China [18]	1984–1986	229/229 (population)	18–70
Beijing, China [19]	1984–1986	112/224 (community)	all
U.S. Collaborative Study [20]	1956–1986	2,197/8,893 (hospital, community)	all
WHO Collaborative Study [21] (Australia, Chile, China, Israel, Mexico, Philippines, Thailand)	1979–1986	368/2,397 (hospital)	all
Cohort studies^b			
Norway [22]	1953–1991	1,694/1,145,076	20–56
U.S. Nurses' Health Study [23]	1976–1988	260/121,700	30–67

^aSubjects: # cases/# controls (type).

^bSubjects: # cases/# subjects.

Table 71.2
The Associations of Several Major Reproductive Factors with Ovarian Cancer Risk

Factors	Comparison	Association	Comments
Age at menarche	Early vs late	None	No association [7,14,15,23,24] Inverse association [18,25] Positive association [19]
Menstrual patterns	Irregular vs regular periods	None	No association [18,19,26] Inverse association [13]
Parity	Parous vs nulliparous	Reduced risk	Inverse association [7,15,17–19,22,23,27]
	Number of children	Inverse trend	[7]
Age at first birth	Late vs early	None	No association [7,19,23] Positive association [15,27 (no trend)] Inverse association (among uniparous women only) [22]
Ovulatory years	Increasing number	Increased risk	Positive association [14,17,19,26,28,29]
Breastfeeding	Ever vs never	Inconclusive	No association Japanese [17], Chinese [19], WHO International studies [30] Inverse association U.S. [7], Australian studies [31]
Infertility	History vs no history	Inconclusive	Positive association with ovulatory abnormalities [7] (but no increase overall in women without drug use) [32], unexplained infertility [33], and nonhormonal infertility (suggested) [34] No association [35–37]
	Treated vs untreated	Inconclusive	Positive association [7,32] No association [18,33,34,36]
Oral contraceptive use	Ever vs never	Reduced risk	Inverse association [7,23(≥5 years of use),25,38,39] No association [15,19]
	Number of years	Inverse trend	[38]
Tubal ligation	Ever vs never	Reduced risk	Inverse association [7,40–43]
Hysterectomy	Ever vs never	Reduced risk	Inverse association [7,15,40–43]
Age at natural menopause	Late vs early	Inconclusive	No association [7,18,19,23] Positive association [15,24 (suggested)]
Noncontraceptive estrogen use	Ever vs never	Inconclusive	No association [7,16,44] Positive association [12,45,46 (fatal cancer)]

compared with no use. This association held regardless of gravidity, although use of human chorionic gonadotropin (hCG) was not associated with risk. In the cohort of Australian women referred for IVF [33], risk was similar for women who had undergone IVF compared with those who had not. In extended follow-up of the Israeli cohort [37], ovarian cancer risk among women treated with clomiphene was slightly elevated but not statistically different from risk among women who were not treated. Other studies also have not found an association between fertility drugs and risk of ovarian cancer [18,36]. All of these studies have lacked sufficient numbers of ovarian cancer cases that were exposed to fertility drugs and details of fertility drug use. Further research is underway to determine whether ovarian cancer risk is elevated in women who have taken fertility drugs [49].

In the age-specific incidence data, risk declines after menopause. This pattern might suggest that late natural menopause is associated with an increased risk of ovarian cancer, although, in general, the epidemiologic data are not supportive [7,23]. Similarly, most studies of noncontraceptive hormone use and ovarian cancer have not provided strong evidence of an association [7].

C. Nonreproductive Factors

Several potential nonreproductive risk factors for ovarian cancer have been assessed, although no strong or consistent associations have emerged.

1. Diet

An influence of dietary intake on ovarian cancer risk has been proposed but has not been extensively evaluated [50]. Cramer and colleagues hypothesized that galactose consumption in combination with low levels of its key metabolic enzyme, galactose-1-phosphate uridylyltransferase, may be involved in ovarian pathogenesis by increasing gonadotropin levels [51]. They showed that women who had lower enzyme activity and higher consumption of galactose were at higher risk of ovarian cancer, but several other studies have failed to confirm this finding [52,53]. Current research is assessing whether diets high in total or saturated fat may increase risk of ovarian cancer, possibly through a hormonal mechanism [50,54–56]. Positive associations with animal fat intake were demonstrated in several [54–56], but not in all [57,58], studies. While effects of other types of fat, macronutrients, and cholesterol have been investigated, the data available are too scant to conclude whether they are related to risk [50,57–59]. There is some evidence that diets high in fruits and vegetables [50,54,55,57] and in carotenoids such as beta-carotene [58] decrease ovarian cancer risk, but more studies are needed.

Various, largely inconsistent, associations have been reported for coffee and alcohol consumption, which are studied more easily than other dietary factors. Moderate to heavy coffee consumption has been associated with an increased risk of ovarian cancer in some studies [60], but most studies indicate no increase in risk [15,16,56,57,61,62]. A positive association with alcohol consumption has been suggested in some studies [16,63,64] but has not been confirmed in others [15,56,57,60,65].

2. Body Size

The relationship of body size with ovarian cancer risk is quite unclear. Results from the combined U.S. studies [7] found conflicting results that depended on the source of controls; relative weight was inversely associated with risk when cases were compared with hospital controls and positively associated with risk when population controls were used. Additional studies show some increase in risk with increasing levels of weight adjusted for height [29,66], but other data indicate no association [16,18,58]. One study found that risk decreased with increasing weight after adjustment for height [57]. Height does not appear to be related to risk [16,18,26].

3. Smoking

Smoking does not appear to be an important risk factor for ovarian cancer [15,16,56,57,60,63].

4. Talc

An excess risk of ovarian cancer mortality observed among occupational cohorts of women exposed to asbestos (reviewed in Weiss *et al.* [67]) raised concern over whether talc exposure might also increase risk. Talc and asbestos share certain physical properties, and talc is sometimes contaminated with asbestos particles. Talc applied to undergarments, sanitary napkins, diaphragms, or directly to the perineal area may subsequently migrate to the peritoneal cavity and ovaries. Most [12,19,41,60,68–70], but not all [71,72], studies show an increase in risk of ovarian cancer with talc use. Risk appears to be associated primarily with the direct application of talc to the perineum and not with other sources of exposure. Trends with duration [41,60,69], frequency [60,70], and age at first use [41,70] have generally not been observed, however, raising doubt about whether the association with talc is real.

5. Antidepressant and Analgesic Drugs

Antidepressants have been speculated to increase ovarian cancer risk through possible effects on estrogen and gonadotropin levels. An early Greek study [16] found that women with ovarian cancer were more likely to have used psychotropic drugs than were controls, but a subsequent study of Greek women [72] failed to confirm those findings. A U.S. case-control study [73] found that self-reported prior use for 1–6 months of both antidepressants and benzodiazepine tranquilizers was associated with an increased risk. Elevated risks were confined to first use that occurred before age 50 and that occurred at least 10 years prior to diagnosis. These findings were corroborated in another case-control study [74] that showed that the association was primarily found with psychotropic drugs operating through dopaminergic, or gabaergic mechanisms rather than through serotonergic pathways.

A U.S. study [75] found a significant decrease in ovarian cancer risk among women who used paracetamol (acetaminophen) and the effect was most marked for frequent and long-term use. Risk associated with aspirin use was also reduced, although the reduction was not statistically significant, and no association was found for ibuprofen or prescribed analgesics. Some findings suggest that the effect of paracetamol on ovarian cancer risk may be mediated through lowered gonadotropin levels [76].

6. Mumps

Mumps and other viruses typically encountered in childhood appear not to be related to risk. The mumps virus has been investigated because of its potential to damage the ovaries and cause premature menopause [77]. Several early studies suggested that history of mumps infection was less common in women with ovarian cancer [78] and that subclinical cases of mumps were more likely [79]. Cramer [77] reported that postmenopausal, but not premenopausal, women with ovarian cancer were less likely to have a history of mumps. Other studies, however, have found little difference in history of mumps infection between cases and controls as assessed by self-report [63,80,81] and by serological evidence [82].

7. Occupational and Other Environmental Exposures

Women employed as hairdressers or cosmetologists may have a small excess risk of ovarian cancer [83]. An elevated ovarian cancer risk among women who frequently dye their hair was also noted in a recent Greek study [72] but not in an earlier one [16].

While data on atomic bomb survivors demonstrate some excess risk of ovarian cancer in women who were less than 50 at the time of exposure, studies seem to indicate that there should be little concern over the amount of radiation to which women are commonly exposed (reviewed in Weiss *et al.* [67]). Likewise, women occupationally exposed to high levels of asbestos through employment in the assembly of gas masks or in an asbestos factory have been shown to have an excess risk of ovarian cancer, but exposure to lower levels is probably not an important determinant of risk [67].

D. Possible Common Pathways

The etiology of ovarian cancer is not established but several theories have been offered. The “incessant ovulation hypothesis,” first suggested by Fathalla [84], posits that epithelial neoplasms result from repeated ovulation, causing minor trauma to the ovarian epithelium and predisposing it to malignant transformation. By this theory, periods of anovulation should be protective. Indeed, risk of ovarian cancer is lower in parous women and women who have used oral contraceptives, and has been shown, with some exceptions, to increase with various markers of ovulatory time (roughly calculated as age at menopause less age at menarche, and total time pregnant, breastfeeding, or using oral contraceptives) [14,17,19,26,28,29]. However, the magnitude of diminished risk associated with the individual components of the composite measure of anovulatory time appears to be greater than that predicted solely by anovulatory periods, suggesting that other mechanisms may also be important [85]. The ovulation hypothesis predicts that women who ovulate infrequently should have a decreased risk of ovarian cancer; however, either no difference or *increased* risks of ovarian cancer have been observed among infertile women in previous studies.

One proposed mechanism to explain the protection afforded by tubal ligation and hysterectomy is the prevention of ovarian exposure to exogenous carcinogenic agents (*e.g.*, talc) that enter the peritoneal cavity through the vagina. Another explanation is that surgery compromises blood flow to the ovaries, leading to involution, fewer cell divisions, and reduced risk. A third expla-

nation is that surgery is accompanied by surveillance and early removal of at-risk ovaries [86].

A hypergonadotropic state (elevated gonadotropin levels) also has been suggested as an etiologic factor for ovarian cancer pathogenesis based on experimental studies in animals relating high gonadotropin production with ovarian tumors [87]. Cramer [88] proposed a model in which persistent gonadotropin stimulation of the ovary predisposes it to the development of malignancy. Few studies have assessed directly the relation of gonadotropin levels to risk, although in one study, *low* serum gonadotropin levels were associated with an increased risk of ovarian cancer [89]. Decreased risks associated with pregnancy, oral contraceptive use, and possibly breastfeeding—factors associated with lower gonadotropin levels—provide some support for this hypothesis. However, these factors are also associated with temporary cessation of ovulation and are consistent with the hypothesis that anovulatory periods are protective against risk. The gonadotropin hypothesis would predict that women with specific types of infertility associated with gonadotropin levels should have an altered risk, and women who took fertility drugs (which either stimulate endogenous gonadotropin release or are gonadotropins themselves) might also be at increased risk. As stated earlier, the effects of specific types of infertility and ovulation induction drugs on ovarian cancer risk are inconclusive as yet. A reduced risk of ovarian cancer would be expected with use of noncontraceptive exogenous hormones because the normally elevated gonadotropin levels associated with the peri- and postmenopausal period are decreased with use [90]. The data on noncontraceptive hormones at present, however, do not consistently support this hypothesis.

V. Future Research Directions

Primary prevention requires better understanding of the etiology of ovarian cancer. Three well-established epidemiologic observations suggest promising strategies for prevention and require further epidemiologic investigation in the near term. Oral contraceptive pills reduce risk, at least in the formulations most commonly used in past decades. A family history of ovarian cancer and, to a lesser extent, breast cancer identifies women at moderately increased risk. Presence of a mutation in BRCA1 or BRCA2 identifies women at markedly increased risk. Thus, one clear priority for epidemiologic research is to assess the effect of oral contraceptives in high-risk women. In addition, further epidemiologic and pharmacologic research is needed to formulate agents like oral contraceptives to reduce risk of ovarian cancer while not increasing risk of other diseases. Continuing genetic studies in women in high-risk families are needed to discover whether genes other than BRCA1 and BRCA2 can be linked to ovarian cancer. When the normal functions of BRCA1 and BRCA2 are known, the mechanisms that underlie the non-genetic risk factors (*e.g.*, repeated ovulation) also will be clearer. Thus, genetic epidemiology will raise many new hypotheses in the next few years. In general, numerous interdisciplinary and translational studies can be expected, even in the absence of a unified etiologic understanding.

Additional priorities for epidemiologic research are suggested by several new leads and several older, unresolved issues. The effects of infertility and of therapies used to treat

infertility will require large and detailed studies. Resolution of the possible link to talcum powder and other physical contaminants in the reproductive tract may require data collected before diagnosis, that is, from cohorts, because the reported effects are modest, inconsistent, and uncertain because of possible recall errors. The investigation of hormonal influences will proceed partly in association with related work in breast and endometrial cancer, partly for practical reasons and partly because the similarities and differences among the three cancers will aid in the interpretation of measured hormonal effects. Even though few strong or clear effects of diet on ovarian cancer have emerged, diet will draw attention if a clean link to breast cancer is defined. Dietary effects and hormonal effects may be related, via body mass index, and various genetic polymorphisms influence metabolism of food and of hormones.

One of the major hypotheses for ovarian carcinogenesis involves persistent gonadotropin stimulation of the ovary, yet little work has been done in directly assessing the relation of gonadotropin levels to ovarian cancer risk. Research in this area has been hindered by the potential for "disease effects" whereby changes in hormone levels are a consequence of the tumor itself. This is particularly problematic for a disease in which a high proportion of cases are diagnosed at late stage. Ideally, hormone levels would be measured several years in advance of the advent of cancer. This may only be achieved in a prospective study with a very large number of subjects. Alternatively, hormone measurements could be made in women with a marker highly predictive of future ovarian cancer development. At present, however, such a marker has not been identified. In the meantime, studies are limited to factors associated with gonadotropin levels such as pregnancy and oral contraceptive use.

Secondary prevention, through detection of early cancers, seems particularly desirable because ovarian cancers are often detected late in the course of development when therapy is less effective. Ongoing trials of screening for ovarian cancer may reveal whether ultrasound and serum assays, alone or in combination [6], can reduce ovarian cancer mortality in postmenopausal women in general or in those at highest risk [91]. Various serum markers are being investigated as prognostic tools, most successfully CA-125 [92].

References

- Ries, L. A. G., Kosary, C. L., Hankey, B. F., Miller, B. A., Hurray, A., and Edwards, B. K., eds. (1997). "SEER Cancer Statistics Review, 1973-1994," NIH Publ. No. 97-2789. National Cancer Institute, Bethesda, MD.
- Kurman, R. J., ed. (1994). "Blaustein's Pathology of the Female Genital Tract," 4th ed. Springer-Verlag, New York.
- Scully, R. E. (1995). Pathology of ovarian cancer precursors. *J. Cell. Biochem., Suppl.* **23**, 208-218.
- Gershenson, D. M., Tortolero-Luna, G., Malpica, A., Baker, V. V., Whittaker, L., Johnson, E., and Mitchell, M. F. (1996). Ovarian intraepithelial neoplasia and ovarian cancer. *Obstet. Gynecol. Clin. North Am.* **23**, 475-543.
- Bourne, T. H., Campbell, S., Reynolds, K. M., Whitehead, M. I., Hampson, J., Royston, P., Crayford, T. J. B., and Collins, W. P. (1993). Screening for early familial ovarian cancer with transvaginal ultrasonography and colour blood flow imaging. *Br. Med. J.* **306**, 1025-1029.
- Jacobs, I., Davies, A. P., Bridges, J., Stabile, I., Fay, T., Lower, A., Grudzinskas, J. G., and Oram, D. (1993). Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *Br. Med. J.* **306**, 1030-1034.
- Whittemore, A. S., Harris, R., Itnyre, J., and the Collaborative Ovarian Cancer Group (1992). Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 U.S. case-control studies. II. Invasive epithelial ovarian cancers in white women. *Am. J. Epidemiol.* **136**, 1184-1203.
- Harvey, E. B., and Brinton, L. A. (1985). Second cancer following cancer of the breast in Connecticut, 1935-82. In "Multiple Primary Cancers in Connecticut and Denmark" (J. D. Boice, R. E. Curtis, R. A. Kleinerman, H. H. Storm, O. M. Jensen, H. S. Jensen, J. T. Flannery, and J. F. Fraumeni, eds.), NIH Publ. No. 85-2714. National Cancer Institute, Bethesda, MD.
- Miki, Y., Swensen, J., Shattuck-Eidens, D., et al. (1994). Isolation of BRCA1, the 17q-linked breast and ovarian cancer susceptibility gene. *Science* **266**, 66-71.
- Wooster, R., Neuhausen, S. L., Mangion, J., Quirk, Y., Ford, D., Collins, N., Nguyen, K., Seal, S., Tran, T., and Averill, D. (1994). Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* **265**, 2088-2090.
- Struwing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., Timmerman, M. M., Brody, L. C., and Tucker, M. A. (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N. Engl. J. Med.* **336**, 1401-1408.
- Booth, M., Beral, V., and Smith, P. (1989). Risk factors for ovarian cancer: A case-control study. *Br. J. Cancer* **60**, 592-598.
- Parazzini, F., La Vecchia, C., Negri, E., and Gentile, A. (1989). Menstrual factors and the risk of epithelial ovarian cancer. *J. Clin. Epidemiol.* **42**, 443-448.
- Franceschi, S., La Vecchia, C., Helmrich, S. P., Mangioni, C., and Tognoni, G. (1982). Risk factors for epithelial ovarian cancer in Italy. *Am. J. Epidemiol.* **115**, 714-719.
- Polychronopoulou, A., Tzonou, A., Hsieh, C.-C., Kaprinis, G., Rebelakos, A., Toupadaki, N., and Trichopoulos, D. (1993). Reproductive variables, tobacco, ethanol, coffee and somatometry as risk factors for ovarian cancer. *Int. J. Cancer* **55**, 402-407.
- Tzonou, A., Day, N. E., Trichopoulos, D., Walker, A., Saliarakis, M., Papapostolou, M., and Polychronopoulou, A. (1984). The epidemiology of ovarian cancer in Greece: A case-control study. *Eur. J. Cancer Clin. Oncol.* **20**, 1045-1052.
- Mori, M., Harabuchi, I., Miyake, H., Casagrande, J. T., Henderson, B. E., and Ross, R. K. (1988). Reproductive, genetic and dietary risk factors for ovarian cancer. *Am. J. Epidemiol.* **128**, 771-777.
- Shu, X.O., Brinton, L. A., Gao, Y. T., and Yuan, J. M. (1989). Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res.* **49**, 3670-3674.
- Chen, Y., Wu, P.-C., Lang, J.-H., Ge, W.-J., Hartge, P., and Brinton, L. A. (1992). Risk factors for epithelial ovarian cancer in Beijing, China. *Int. J. Epidemiol.* **21**, 23-29.
- Whittemore, A. S., Harris, R., Itnyre, J., Halpern, J., and the Collaborative Ovarian Cancer Group (1992). Characteristics relating to ovarian cancer risk: Collaborative analysis of 12 U.S. case-control studies. I. Methods. *Am. J. Epidemiol.* **136**, 1175-1183.
- The WHO Collaborative Study of Neoplasia and Steroid Contraceptives (1989). Epithelial ovarian cancer and combined oral contraceptives. *Int. J. Epidemiol.* **18**, 538-545.
- Albrektzen, G., Heuch, I., and Kvåle, G. (1996). Reproductive factors and incidence of epithelial ovarian cancer: A Norwegian prospective study. *Cancer Causes Control* **7**, 421-427.
- Hankinson, S. E., Colditz, G. A., Hunter, D. J., Willett, W. C., Stampfer, M. J., Rosner, B., Hennekens, C. H., and Speizer, F. E.

- (1995). A prospective study of reproductive factors and risk of epithelial ovarian cancer. *Cancer (Philadelphia)* **76**, 284–290.
24. Franceschi, S., La Vecchia, C., Booth, M., Tzonou, A., Negri, E., Parazzini, F., Trichopoulos, D., and Beral, V. (1991). Pooled analysis of 3 European case-control studies of ovarian cancer: II. Age at menarche and at menopause. *Int. J. Cancer* **49**, 57–60.
 25. Tavani, A., Negri, E., Franceschi, S., Parazzini, F., and La Vecchia, C. (1993). Risk factors for epithelial ovarian cancer in women under age 45. *Eur. J. Cancer* **29A**, 1297–1301.
 26. Hildreth, N. G., Kelsey, J. L., LiVolsi, V. A., Fischer, D. B., Holford, T. R., Mostow, E. D., Schwartz, P. E., and White, C. (1981). An epidemiologic study of epithelial carcinoma of the ovary. *Am. J. Epidemiol.* **114**, 398–405.
 27. Negri, E., Franceschi, S., Tzonou, A., Booth, M., La Vecchia, C., Parazzini, F., Beral, V., Boyle, P., and Trichopoulos, D. (1991). Pooled analysis of 3 European case-control studies of ovarian cancer: I. Reproductive factors and risk of epithelial ovarian cancer. *Int. J. Cancer* **49**, 50–56.
 28. Wu, M. L., Whittemore, A. S., Paffenbarger, R. S., Sarles, D. L., Kampert, J. B., Grosser, S., Jung, D. L., Ballon, S., Hendrickson, M., and Mohle-Boetani, J. (1988). Personal and Environmental characteristics related to epithelial ovarian cancer. I. Reproductive and menstrual events and oral contraceptive use. *Am. J. Epidemiol.* **128**, 1216–1227.
 29. Casagrande, J. T., Pike, M. C., Ross, R. K., Louise, E. W., Roy, S., and Henderson, B. E. (1979). "Incessant ovulation" and ovarian cancer. *Lancet*, July 28, pp. 170–172.
 30. Rosenblatt, K. A., Thomas, D. B., and The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives (1993). Lactation and the risk of epithelial ovarian cancer. *Int. J. Epidemiol.* **22**, 192–197.
 31. Siskind, V., Green, A., Bain, C., and Purdie, D. (1997). Breastfeeding, menopause and epithelial ovarian cancer. *Epidemiology* **8**, 188–191.
 32. Rossing, M. A., Daling, J. R., Weiss, N. S., Moore, D. E., and Self, S. G. (1994). Ovarian tumors in a cohort of infertile women. *N. Engl. J. Med.* **331**, 771–776.
 33. Venn, A., Watson, L., Lumley, J., Giles, G., King, C., and Healy, D. (1995). Breast and ovarian cancer incidence after infertility and in vitro fertilisation. *Lancet* **346**, 995–1000.
 34. Ron, E., Lunenfeld, B., Menczer, J., Blumstein, T., Katz, L., Oelsner, G., and Serr, D. (1987). Cancer incidence in a cohort of infertile women. *Am. J. Epidemiol.* **125**, 780–790.
 35. Brinton, L. A., Melton, J., Malkasian, G. D., Bond, A., and Hoover, R. (1989). Cancer risk after evaluation for infertility. *Am. J. Epidemiol.* **129**, 712–722.
 36. Franceschi, S., La Vecchia, C., Negri, E., Guarneri, S., Montella, M., Conti, E., and Parazzini, F. (1994). Fertility drugs and risk of epithelial ovarian cancer in Italy. *Hum. Reprod.* **9**, 1673–1675.
 37. Modan, B., Ron, E., Lerner-Geva, L., Blumstein, T., Menczer, J., Rabinovici, J., Oelsner, G., Freedman, L., Mashiach, S., and Lunenfeld, B. (1998). Cancer incidence in a cohort of infertile women. *Am. J. Epidemiol.* **147**, 1038–1042.
 38. Hankinson, S. E., Colditz, G. A., Hunter, D. J., Spencer, T. L., Rosner, B., and Stampfer, M. J. (1992). A quantitative assessment of oral contraceptive use and risk of ovarian cancer. *Obstet. Gynecol.* **80**, 708–714.
 39. Rosenberg, L., Palmer, J. R., Zauber, A. G., Warshauer, M. E., Lewis, J. L., Strom, B. L., Harlap, S., and Shapiro, S. (1994). A case-control study of oral contraceptive use and invasive epithelial ovarian cancer. *Am. J. Epidemiol.* **139**, 654–661.
 40. Rosenblatt, K. A., Thomas, D. B., and The World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives (1996). Reduced risk of ovarian cancer in women with a tubal ligation or hysterectomy. *Cancer Epidemiol., Biomarkers Prev.* **5**, 933–935.
 41. Green, A., Purdie, D., Bain, C., Siskind, V., Russell, P., Quinn, M., Ward, B., and the Survey of Women's Health Study Group (1997). Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *Int. J. Cancer* **71**, 948–951.
 42. Krieger, N., Sloan, M., Cotterchio, M., and Parsons, P. (1997). Surgical procedures associated with risk of ovarian cancer. *Int. J. Epidemiol.* **26**, 710–715.
 43. Hankinson, S. E., Hunter, D. J., Colditz, G. A., Willett, W. C., Stampfer, M. J., Rosner, B., Hennekens, C. H., and Speizer, F. E. (1993). Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *J. Am. Med. Assoc.* **270**, 2813–2818.
 44. Annegers, J. F., O'Fallon, W., and Kurland, L. T. (1977). Exogenous oestrogens and ovarian cancer. *Lancet*, October 22, pp. 869–870.
 45. Hoover, R., Gray, L. A., and Fraumeni, J. F. (1977). Stilboestrol (diethylstilbestrol) and the risk of ovarian cancer. *Lancet*, September 10, pp. 533–534.
 46. Rodriguez, C., Calle, E. E., Coates, R. J., Miracle-McMahill, H. L., Thun, M. J., and Health, C. W. (1995). Estrogen replacement therapy and fatal ovarian cancer. *Am. J. Epidemiol.* **141**, 828–835.
 47. Nasca, P. C., Greenwald, P., Chorost, S., Richart, R., and Caputo, T. (1984). An epidemiologic case-control study of ovarian cancer and reproductive factors. *Am. J. Epidemiol.* **119**, 705–713.
 48. Coulam, C. B., Annegers, J. F., and Kranz, J. S. (1983). Chronic anovulation syndrome and associated neoplasia. *Obstet. Gynecol.* **61**, 403–407.
 49. Kaufman, S. C., Spirtas, R., and Alexander, N. J. (1995). Do fertility drugs cause ovarian tumors? *J. Women's Health* **4**, 247–258.
 50. World Cancer Research Fund/ American Institute for Cancer Research (1997). "Food, Nutrition and the Prevention of Cancer: A Global Perspective." American Institute for Cancer Research, Washington, DC.
 51. Cramer, D. W., Harlow, B. L., Willett, W. C., Welch, W. R., Bell, D. A., Scully, R. E., Ng, W. G., and Knapp, R. C. (1989). Galactose consumption and metabolism in relation to the risk of ovarian cancer. *Lancet*, July 8, pp. 66–71.
 52. Mettlin, C. J., and Piver, M. S. (1990). A case-control study of milk-drinking and ovarian cancer risk. *Am. J. Epidemiol.* **132**, 871–876.
 53. Herrinton, L. J., Weiss, N. S., Beresford, S. A. A., Stanford, J. L., Wolfia, D. M., Feng, Z., and Scott, C. R. (1995). Lactose and galactose intake and metabolism in relation to the risk of epithelial ovarian cancer. *Am. J. Epidemiol.* **141**, 407–416.
 54. La Vecchia, C., Decarli, A., Negri, E., Parazzini, F., Gentile, A., Cecchetti, G., Fasoli, M., and Franceschi, S. (1987). Dietary factors and the risk of epithelial ovarian cancer. *J. Natl. Cancer Inst.* **79**, 663–669.
 55. Shu, X. O., Gao, Y. T., Yuan, J. M., Ziegler, R. G., and Brinton, L. A. (1989). Dietary factors and epithelial ovarian cancer. *Br. J. Cancer* **59**, 92–96.
 56. Cramer, D. W., Welch, W. R., Hutchison, G. B., Willett, W., and Scully, R. E. (1984). Dietary animal fat in relation to ovarian cancer risk. *Obstet. Gynecol.* **63**, 833–838.
 57. Byers, T., Marshall, J., Graham, S., Mettlin, C., and Swanson, M. (1983). A case-control study of dietary and nondietary factors in ovarian cancer. *J. Natl. Cancer Inst.* **71**, 681–686.
 58. Slatery, M. L., Schuman, K. L., West, D. W., French, T. K., and Robison, L. M. (1989). Nutrient intake and ovarian cancer. *Am. J. Epidemiol.* **130**, 497–502.
 59. Tzonou, A., Hsieh, C. C., Polychronopoulou, A., Kaprinis, G., Toupadaki, N., Trichopoulou, A., Karakatsani, A., and Trichopoulos, D. (1993). Diet and ovarian cancer: A case-control study in Greece. *Int. J. Cancer* **55**, 411–414.

60. Whittemore, A. S., Wu, M. L., Paffenbarger, R. S., Sarles, D. L., Kampert, J. B., Grosser, S., Jung, D. L., Ballon, S., and Hendrickson, M. (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am. J. Epidemiol.* **128**, 1228–1240.
61. Hartege, P., Leshner, L. P., McGowan, L., and Hoover, R. (1982). Coffee and ovarian cancer. *Int. J. Cancer* **30**, 531–532.
62. Leviton, A. (1990). Methylxanthine consumption and the risk of ovarian malignancy. *Cancer Lett.* **51**, 91–101.
63. Hartege, P., Schiffman, M. H., Hoover, R., McGowan, L., Leshner, L., and Norris, H. J. (1989). A case-control study of epithelial ovarian cancer. *Am. J. Obstet. Gynecol.* **161**, 10–16.
64. La Vecchia, C., Negri, E., Franceschi, S., Parazzini, F., Gentile, A., and Fasoli, M. (1992). Alcohol and epithelial ovarian cancer. *J. Clin. Epidemiol.* **45**, 1025–1030.
65. Gwinn, M. L., Webster, L. A., Lee, N. C., Layde, P. M., Rubin, G. L., and the Cancer and Steroid Hormone Study Group (1986). Alcohol consumption and ovarian cancer risk. *Am. J. Epidemiol.* **123**, 759–766.
66. Farrow, D. C., Weiss, N. S., Lyon, J. L., and Daling, J. R. (1989). Association of obesity and ovarian cancer in a case-control study. *Am. J. Epidemiol.* **129**, 1300–1304.
67. Weiss, N. S., Cook, L. S., Farrow, D. C., and Rosenblatt, K. A. (1996). Ovarian cancer. In "Cancer Epidemiology and Prevention" (D. Schottenfeld and J. F. Fraumeni, eds.), 2nd ed., pp 1040–1057. Oxford University Press, New York.
68. Cramer, D. W., Welch, W. R., Scully, R. E., and Wojciechowski, C. A. (1982). Ovarian cancer and talc. *Cancer (Philadelphia)* **50**, 372–376.
69. Cook, L. S., Kamb, M. L., and Weiss, N. S. (1997). Perineal powder exposure and the risk of ovarian cancer. *Am. J. Epidemiol.* **145**, 459–465.
70. Harlow, B. L., Cramer, D. W., Bell, D. A., and Welch, W. R. (1992). Perineal exposure to talc and ovarian cancer risk. *Obstet. Gynecol.* **80**, 19–26.
71. Hartege, P., Hoover, R., Leshner, L. P., and McGowan, L. (1983). Talc and ovarian cancer. *J. Am. Med. Assoc.* **250**, 1844.
72. Tzonou, A., Polychronopoulou, A., Hsieh, C.-C., Rebelakos, A., Karakatsani, A., and Trichopoulos, D. (1993). Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int. J. Cancer* **55**, 408–410.
73. Harlow, B. L., and Cramer, D. W. (1995). Self-reported use of antidepressants or benzodiazepine tranquilizers and risk of epithelial ovarian cancer: Evidence from two combined case-control studies (Massachusetts, United States). *Cancer Causes Control* **6**, 130–134.
74. Harlow, B. L., Cramer, D. W., Baron, J. A., Titus-Ernstoff, L., and Greenberg, E. R. (1998). Psychotropic medication use and risk of epithelial ovarian cancer. *Cancer Epidemiol., Biomarkers Prev.* **7**, 697–702.
75. Cramer, D. W., Harlow, B. L., Titus-Ernstoff, L., Bohlke, K., Welch, W. R., and Greenberg, E. R. (1998). Over-the-counter analgesics and risk of ovarian cancer. *Lancet* **351**, 104–107.
76. Cramer, D. W., Liberman, R. F., Hornstein, M. D., McShane, P., Powers, D., Li, E. Y., and Barbieri, R. (1998). Basal hormone levels in women who use acetaminophen for menstrual pain. *Fertil. Steril.* **70**, 371–373.
77. Cramer, D. W., Welch, W. R., Cassells, S., and Scully, R. E. (1983). Mumps, menarche, menopause, and ovarian cancer. *Am. J. Obstet. Gynecol.* **147**, 1–6.
78. Newhouse, M. L., Pearson, R. M., Fullerton, J. M., Boesen, E. A. M., and Shannon, H. S. (1977). A case control study of carcinoma of the ovary. *Br. J. Prev. Soc. Med.* **31**, 148–153.
79. Menczer, J., Modan, M., Ranon, L., and Golan, A. (1979). Possible role of mumps virus in the etiology of ovarian cancer. *Cancer (Philadelphia)* **43**, 1375–1379.
80. McGowan, L., Parent, L., Lednar, W., and Norris, H. J. (1979). The woman at risk for developing ovarian cancer. *Gynecol. Oncol.* **7**, 325–344.
81. Schiffman, M. H., Hartege, P., Leshner, L. P., and McGowan, L. (1985). Mumps and postmenopausal ovarian cancer. *Am. J. Obstet. Gynecol.* **152**, 116–117.
82. Golan, A., Joosting, A. C. C., and Orchard, M. E. (1979). Mumps virus and ovarian cancer. *S. Afr. Med. J.* **56**, 18–20.
83. Boffetta, P., Andersen, A., Lyng, E., Barlow, L., and Pukkala, E. (1994). Employment as hairdresser and risk of ovarian cancer and non-hodgkin's lymphomas among women. *J. Occup. Environ. Med.* **36**, 61–65.
84. Fathalla, M. F. (1971). Incessant ovulation—A factor in ovarian neoplasia? *Lancet*, July 17, p. 163.
85. Risch, H. A., Weiss, N. S., Lyon, J. L., Daling, J. R., and Liff, J. M. (1983). Events of reproductive life and the incidence of epithelial ovarian cancer. *Am. J. Epidemiol.* **117**, 128–139.
86. Weiss, N. S., and Harlow, B. L. (1986). Why does hysterectomy without bilateral oophorectomy influence the subsequent incidence of ovarian cancer? *Am. J. Epidemiol.* **124**, 856–858.
87. McGowan, L., and Davis, R. H. (1970). Intrasplenic ovarian grafts in Syrian hamsters and peritoneal fluid cellular distribution. *Proc. Soc. Exp. Biol. Med.* **134**, 507.
88. Cramer, D. W., and Welch, W. R. (1983). Determinants of ovarian cancer risk. II. Inferences regarding pathogenesis. *J. Natl. Cancer Inst.* **71**, 717–721.
89. Helzlsouer, K. J., Alberg, A. J., Gordon, G. B., Longcope, C., Bush, T. L., Hoffman, S. C., and Comstock, G. W. (1995). Serum gonadotropins and steroid hormones and the development of ovarian cancer. *J. Am. Med. Assoc.* **274**, 1926–1930.
90. Hartege, P., Hoover, R., McGowan, L., Leshner, L., and Norris, H. J. (1988). Menopause and ovarian cancer. *Am. J. Epidemiol.* **127**, 990–998.
91. National Institutes of Health Consensus Development Conference Statement (1994). Ovarian cancer: Screening, treatment, and follow-up. *Gynecol. Oncol.* **55**, S4–S14.
92. Schutter, E. M., Sohn, C., Kristen, P., Mobus, V., Crombach, G., Kaufmann, M., Caffier, H., Kreienberg, R., Verstraeten, A. A., and Kenemans, P. (1998). Estimation of probability of malignancy using a logistic model combining physical examination, ultrasound, serum CA 125, and serum CA 72-4 in postmenopausal women with a pelvic mass: An international multicenter study. *Gynecol. Oncol.* **69**, 56–63.

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Endometrial Cancer

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I. Introduction

Endometrial cancer is a relatively common gynecologic cancer; diagnosis generally occurs after abnormal uterine bleeding or spotting [1]. The five-year relative survival following diagnosis is greater than 84% overall [2], but it varies by the size, spread, and morphology of the cancer. Five-year relative survival is 96 to 100% for women with tumors confined to the uterine body (*i.e.*, Stage I) or highly differentiated tumors (*i.e.*, low grade), but it falls to 27 to 47% with tumors that have spread beyond the pelvis (Stage IV) or are poorly differentiated (*i.e.*, high grade) [2,3].

Current evidence indicates that exposure of the endometrium to high circulating levels of estrogens, especially from exogenous sources, increases the likelihood of developing this disease. The causal role of exogenous estrogens is highlighted by the sharp rise in endometrial cancer incidence in the early 1970s in the U.S. that followed an increase in the use of unopposed estrogens among postmenopausal women. There is also evidence that progestogens (both endogenous and exogenous) have a beneficial effect on the endometrium. The actions of many of the other known or suspected factors that alter endometrial cancer risk, such as obesity, reproductive characteristics, certain medical conditions, and cigarette smoking, may be explained at least in part by their influence on estrogen and progestogen activity.

II. Demographic Patterns of Incidence and Mortality

The body (corpus) of the uterus contains several different types of tissue: the endometrium (the inner mucosal layer); the myometrium (the thick, middle, muscular layer); and the serosa (the thin external coat). The cervix is the lower portion of the uterus that lies below the uterine body. Endometrial cancer occurrence has often been described through the proxy measure of cancer of the corpus uteri. This measure is a relatively good proxy for endometrial cancer; among African-Americans, 75% of cancers of the corpus uteri are endometrial in nature, and among white Americans, the figure is more than 90% [2]. Mortality from endometrial cancer can be estimated from rates for cancer of the uterine corpus or through a combination of rates of cancer of the corpus uteri and uterine cancer, not otherwise specified (NOS). The latter measure is probably the more useful but is nonetheless somewhat inaccurate because a substantial proportion of deaths in the "NOS" category may be due to cervical cancer. This proportion has decreased over time due to diminishing proportions of cervical cancers included in the uterine cancer, NOS category [4] as well as to decreases in cervical cancer mortality [2]. This reduction in cervical cancer mortality complicates interpretation of time trends in mortality for the

combined category of uterine cancers of the corpus plus uterine cancer NOS. Both incidence and mortality rates will also be artificially low, because corrections are not made in routinely available data for the proportion of women who have had their uterus removed and are no longer at risk for developing endometrial cancer. Nonetheless, even with these limitations, we can draw some conclusions about changes and patterns in endometrial cancer incidence and mortality.

A. Time

Rapid changes have occurred in the incidence of endometrial cancer since the 1960s in the United States. The incidence began to rise in the 1960s and reached a peak in the mid-1970s [2,5]. The increase in incidence was experienced primarily by postmenopausal women and was generally greater in the western than in the eastern part of the country (Table 72.1) [5a–5c]. The increase shown in the table is actually an underestimate of the true increase; the rate of hysterectomy for reasons other than

Table 72.1
Annual Incidence of Invasive Carcinoma of the Uterine Corpus by Age: Connecticut and Alameda County, California, 1960–1994^a

Time period	Connecticut: age (years)		Alameda County ^b : age (years)	
	30–49	50–69	30–49	50–69
1960–1964	15.4	66.5	11.0	70.6
1965–1969	13.7	67.9	15.7	109.8
1970–1971	11.6	77.1	17.0	135.6
1972–1973	16.7	84.4	23.2	195.4
1974–1975	14.9	96.2	19.3	186.6
1976–1977	12.6	84.0	12.6	177.6
1978–1979	11.3	79.9	6.7	127.2
1980–1981	11.7	74.2	10.1	110.2
1982–1983	8.6	73.5	9.3	96.8
1984–1985	10.4	69.5	7.6	105.8
1986–1987	11.2	66.3	8.3	88.0
1988–1989	8.7	64.7	8.0	89.3
1990–1991	9.7	69.0	9.9	76.0
1992–1993	12.5	75.9	7.0	62.5
1994	11.8	72.5	8.1	65.3

Personal communications and National Cancer Institute.

^aRate per 100,000 adjusted, within the broad age groups shown, to a uniform standard (10-year age groups for Connecticut, 5-year age groups for Alameda County). Data compiled from [5a,5c].

^bWhites only.