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Prospective on Ovarian Cancer: Why Prevent?

William J. Hoskins, MD

Department of Surgery, Avon Chair of Gynecologic Oncology Research, Memorial Sloan-Kettering Cancer Center, New York, NY 10021

Abstract In 1995, an estimated 26,600 women in the United States will be diagnosed with ovarian cancer. During that same year, approximately 14,500 women will die from the disease. Although ovarian cancer accounts for only 33% of the gynecologic cancers and only 5% of all cancers affecting women in the United States, it results in 55% of the deaths from gynecologic cancer and 6% of the cancer deaths in women. The cure rate for ovarian cancer by stage at diagnosis is not significantly different from other gynecologic cancers. Ovarian cancer confined to the ovary (Stage I) can be cured in 90% of cases. Survival for patients with advanced disease (Stages III and IV) is 21%.

Unfortunately, while 73% of endometrial cancers, 55% of breast cancers, and 50% of cervical cancers are diagnosed as Stage I, only 23% of ovarian cancers are diagnosed as Stage I. Thus, five-year survival for all endometrial cancer is 85%, for all breast cancer, 82%, for cervical cancer, 70%, and for ovarian cancer, only 42%. The lack of early symptoms and the absence of any proven method of screening for early ovarian cancer results in over 70% of women being diagnosed after the disease has spread beyond the ovary. Also, unlike breast, cervical, and endometrial cancer, there is no known premalignant phase for ovarian cancer; therefore, diagnosis and treatment of a premalignant condition to prevent the development of ovarian cancer is not possible. Theories to explain the development of ovarian cancer are based on observations that ovulation inhibition through pregnancy, oral contraceptive use, and a shorter ovulatory period (late menarche or early menopause) result in a decreased incidence of ovarian cancer. The incessant disruption of the ovarian capsule followed by repair may provide the opportunity for aberrant growth. Finally, therapy of women with ovarian cancer usually requires multiple surgical procedures, multiple courses of chemotherapy, and results in significant morbidity and health care costs. For most women with the disease, the end result will still be a slow, painful death by starvation. There should be little doubt based on the above statistics that every effort should be directed towards prevention of ovarian cancer. Possible strategies in the prevention of ovarian cancer should be directed towards determining if a premalignant condition exists, developing screening tools to detect premalignant disease or disease confined to the ovary, and developing interventions to prevent the development of the disease. It is well established that use of oral contraceptives for five or more years can result in up to a 50% reduction in the occurrence of epithelial ovarian cancer. Given the low complication rates from oral contraceptive use, this medication should be considered as a method of prevention, especially in high-risk groups. In addition, this is a realistic starting point for research into the development of preventive regimens.

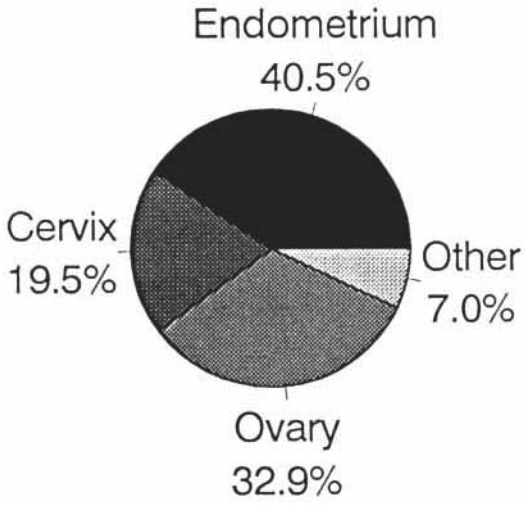
Key words: Cancer, ovarian, prevention

Send correspondence to Dr. William J. Hoskins, MD, Chief, Gynecology Service, Department of Surgery, Avon Chair of Gynecologic Oncology Research, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

In 1995, an estimated 26,600 women will be diagnosed with ovarian cancer and approximately 14,500 women will die of the disease. Although ovarian cancer accounts for only 33% of female genital cancers, it accounts for 55% of the deaths from these diseases [1] (Fig. 1). In

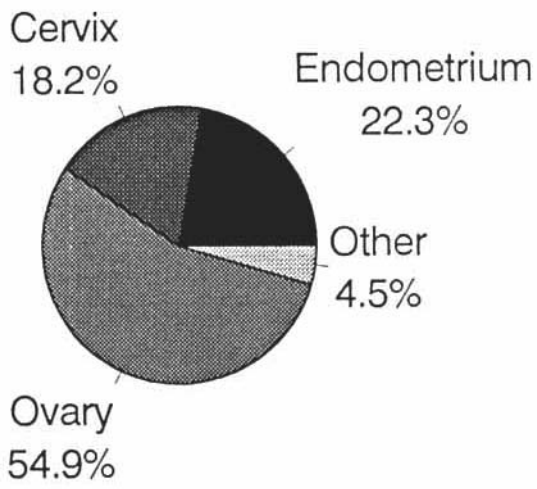
Gynecologic Cancers: 1995

New Cancer Cases



Endometrium:	**32800**
Cervix	**15800**
Ovary	**26600**
Other	**5700**
Total	**80900**

Estimated Cancer Deaths



Endometrium	**5900**
Cervix	**4800**
Ovary	**14500**
Other	**1200**
Total	**26400**

Fig. 1. Estimated new cases of gynecologic cancers and estimated deaths from gynecologic cancers in 1995 [1].

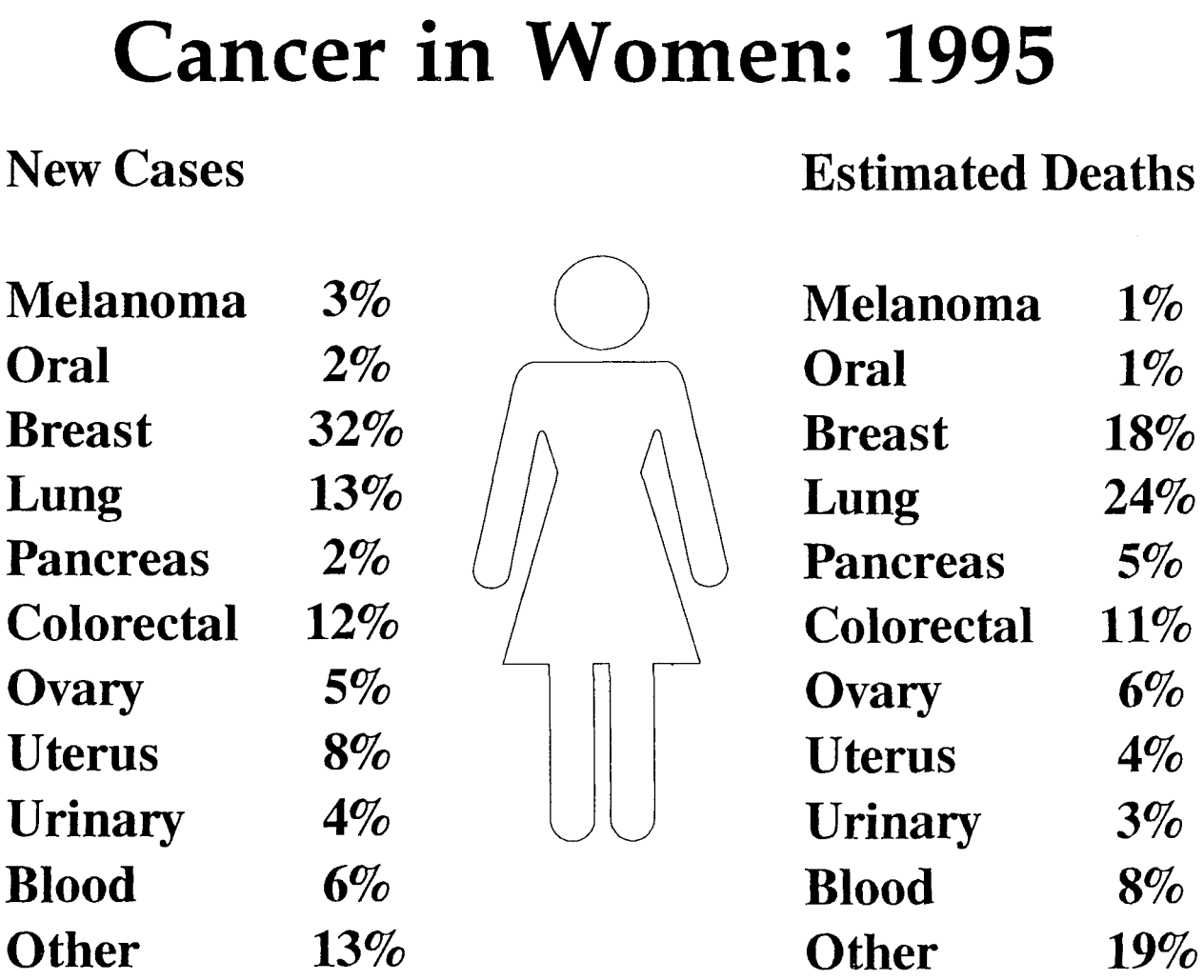


Fig. 2. Estimated new cases of all cancers in women and estimated deaths from all cancers in women for 1995 [1].

1995, based on previous statistics, ovarian cancer will account for 5% of new cases of cancer in women and will cause 6% of the deaths. Ovarian cancer is the fourth leading cause of solid tumor cancer deaths among women, following, in order, lung, breast, and colorectal cancer (Fig. 2).

Figure 3 shows the age-specific incidence of ovarian cancer by race in the United States. As can be seen, the incidence rises from about 2 per 100,000 at age 20 to about 50 per 100,000 in women at age 65. The incidence peaks about age 65 to 70 and thereafter remains stable. The average annual age-adjusted incidence in 1987 was 13.7 per 100,000 [2]. African-American women have a slightly lower incidence at all ages.

Table I illustrates the risk factors for ovarian cancer. A longer period of ovarian function as manifested by early menarche and late menopause is associated with increased risk, as is a history of infertility. Table II shows the age-standardized incidence of ovarian cancer by geography and illustrates the increased incidence among White women of North American or Northern European extraction [3]. The disease is also more frequent in women of industrialized countries (except Japan).

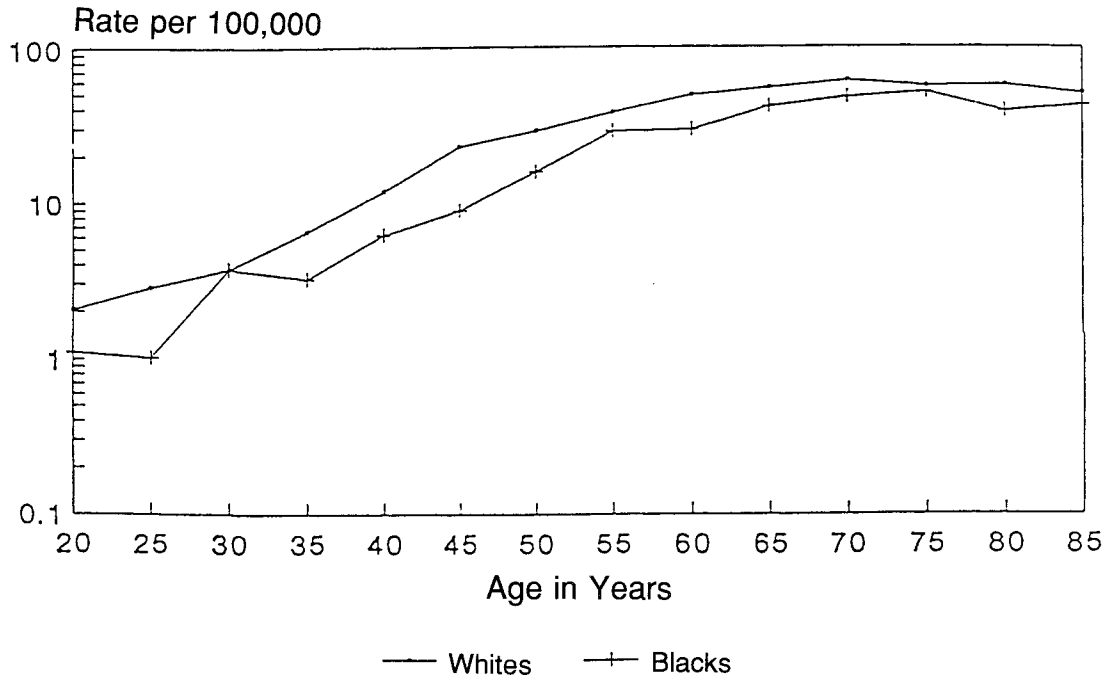


Fig. 3. Age-specific incidence of cancer of the ovary by race.

One of the most significant risk factors is a family history of ovarian cancer. A single family member with ovarian cancer increases the relative risk from 2.9–3.6-fold, or an increase in the lifetime risk from 1.4% to about 5–6% [4,5]. In addition, there are three recognized hereditary familial ovarian cancer syndromes: site-specific ovarian cancer syndrome, breast-ovarian cancer syndrome, and the Lynch II syndrome (hereditary non-polyposis colon cancer plus a variety of other adenocarcinomas including ovarian cancer) [6]. Female members of one of these cancer families have a 50% chance of carrying the gene and thus a 40–50% chance of developing the disease. Because of incomplete penetrance, not all women with the gene will be afflicted with the disease, but a woman shown to have the gene (as will probably be the case soon with BRCA-1) will have a lifetime disease risk in excess of 80%. However, hereditary syndromes probably account for only 5–10% of all ovarian cancers. The vast majority of ovarian cancers are sporadic.

As illustrated in Figure 4, the cure rate for ovarian cancers localized to the ovary is about 90%. However, the cure rate for distant disease (Stage III and IV) is only 29%. Actually, the cure rates for ovarian cancer confined to the ovary are quite similar to breast, colorectal, and uterine cancer (corpus and cervix). The overall survival is 42% (Table III), with a statistically significant increase in survival between 1980–1982 and 1983–1990. Unfortunately, as shown in Figure, only 23% of ovarian cancers are diagnosed while confined to the ovary; 52% are diagnosed with distant disease (Stage III or IV). Again, comparison of stage at diagnosis with breast, colorectal, and uterine cancer is striking (Fig. 5), and demonstrates why the overall survival for those cancers is so much better than that of ovarian cancer.

After prevention, the second most important factor in the curability of most cancers is early diagnosis. Few ovarian cancers are diagnosed early. Comparison to the other cancers illustrated in Figures 3 and 4 is in order. Mammographic screening combined with clinical examination and self-examination results in early diagnosis of over 50% of breast cancers. Pap smears result in 50% of cervical cancers being diagnosed as Stage I. The presence of an early warning sign

TABLE I. Epidemiology of Ovarian Cancer [2]

Risk Factor	Relative Risk
Older age	3.0
North America, Northern Europe	2.0–5.0
Higher level education, income	1.5–2.0
White race	1.5
Nulligravidity	2.0–3.0
History of infertility	2.0–5.0
Early menarche	1.5
Late menopause	1.5–2.0
Hysterectomy	0.5–0.7
Use of oral contraceptives	0.3–0.5
Perineal talc exposure	1.5–2.0
Relative with ovarian cancer	3.0–4.0

TABLE II. Ovarian Cancer: Geographic Incidence Age-Standardized Average Incidence Rate per 100,000 [15]

Country	Rate per 100,000
Sweden	14.9
Israel (born in U.S. or Europe)	14.3
Canada (British Columbia)	13.8
U.S. (San Francisco)	13.3
Israel (all Jews)	12.6
U.S. (Connecticut)	12.2
Germany	11.8
New Zealand	11.3
United Kingdom	11.1
Canada (Quebec)	9.4
Israel (born in Israel)	8.7
Brazil	6.1
Israel (born in Africa or Asia)	5.8
India	4.6
Japan	2.7

Percent Five-Year Relative Survival by Stage: 1983–1990

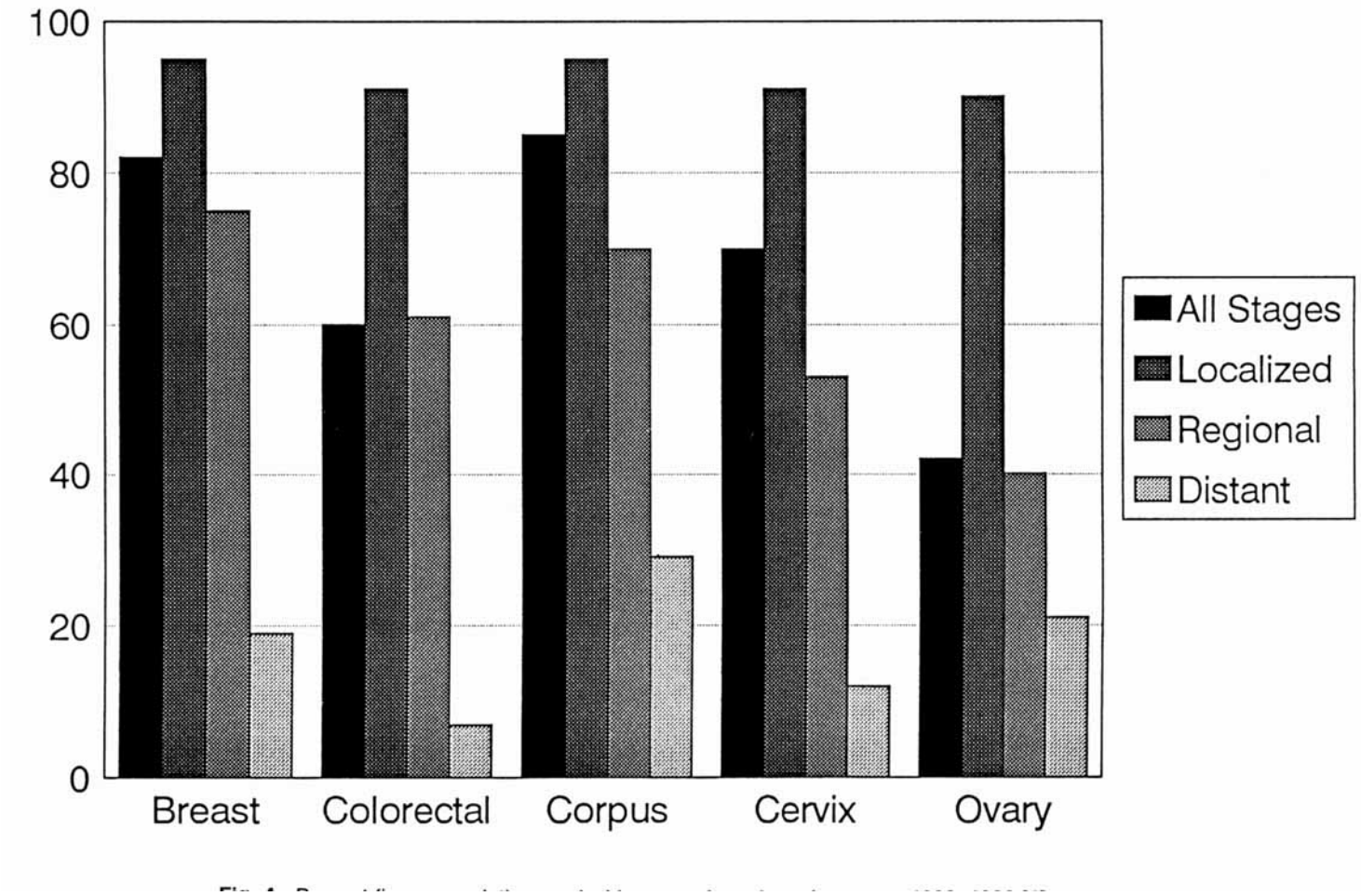


Fig. 4. Percent five-year relative survival by stage for selected cancers: 1983–1990 [1].

TABLE III. Trends in Cancer Survival by Race and Year of Diagnosis [1]

Site	1974–1976	1980–1982	1983–1990
	White/Black	White/Black	White/Black
Breast	75/63	77/66	82*/66*
Colon	50/56	56/49	61*/50*
Corpus	89/60	83/54	85**/55
Cervix	69/63	68/60	70/56**
Ovary	36/40	39/38	42*/38

* Statistically significant increase between 1974–1976 and 1983–1990; ** Statistically significant decrease between 1974–1976 and 1983–1990.

(abnormal bleeding) results in 73% of endometrial cancers being diagnosed early. Even in colorectal cancer, screening with fecal occult blood tests and sigmoidoscopy, as well as the early investigation of rectal bleeding, results in the early diagnosis of 37% of cancers when they are localized. Unfortunately, there are no proven screening tests for ovarian cancer. After a thorough evaluation of the data concerning screening for ovarian cancer with serum CA-125 testing and/or transvaginal ultrasound, the National Institutes of Health Consensus Conference on Ovarian Cancer issued the following statement: "There is no evidence available yet that the current screening modalities of CA-125 and transvaginal ultrasound can be effectively used for widespread screening to reduce mortality from ovarian cancer nor that their use will result in decreased morbidity and mortality" [7].

Ovarian cancer therapy requires an initial cytoreductive surgical procedure that includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy, as a minimum. In most cases of advanced disease, the removal of tumor implants from the abdominal cavity (tumor debulking) is required and it may be necessary to resect portions of the urinary tract and/or gastrointestinal tract. In some cases, extensive lymphadenectomy is also required. Although common in the past, creation of permanent diversions of the intestinal tract, usually in the form of a colostomy, are rarely performed in most centers experienced in the surgical therapy of ovarian cancer. The availability of methods for very low rectal anastomosis and improvements in chemotherapy usually make intestinal diversions avoidable. Nevertheless, the surgical procedure for advanced ovarian cancer is one of the most difficult procedures undertaken by the gynecologic oncologist and is associated with significant morbidity and occasional mortality. In experienced centers, approximately one-half of patients with advanced ovarian cancer can undergo optimal cytoreduction, which is usually defined as residual disease with a diameter of 2 cm or less. Survival of patients with advanced ovarian cancer is directly related to the diameter of the largest residual disease, as illustrated in Figure 6 [8].

Following initial cytoreductive surgery, most patients with ovarian cancer will require chemotherapy. Table IV illustrates some major clinical trials of the Gynecologic Oncology Group and shows the modest improvement from introducing cisplatin and paclitaxel [9–12]. Today, we can expect overall response rates of 70–80% with multi-agent chemotherapy. Despite these excellent response rates, only 40–50% of patients will achieve a complete clinical response (no clinical evidence of disease), and only 20–25% will have a complete pathologic response (negative second-look laparotomy). Since even those 25% of patients with a negative second look will experience a 35–45% recurrence rate within five years, it is clear that about 85% of patients with advanced ovarian cancer will not be cured by the initial surgery and chemotherapy and will require some type of salvage therapy. Of those patients requiring salvage therapy, only a few will eventually be cured of their disease.

Percent of Cancer Cases by Stage at Diagnosis: 1983–1990

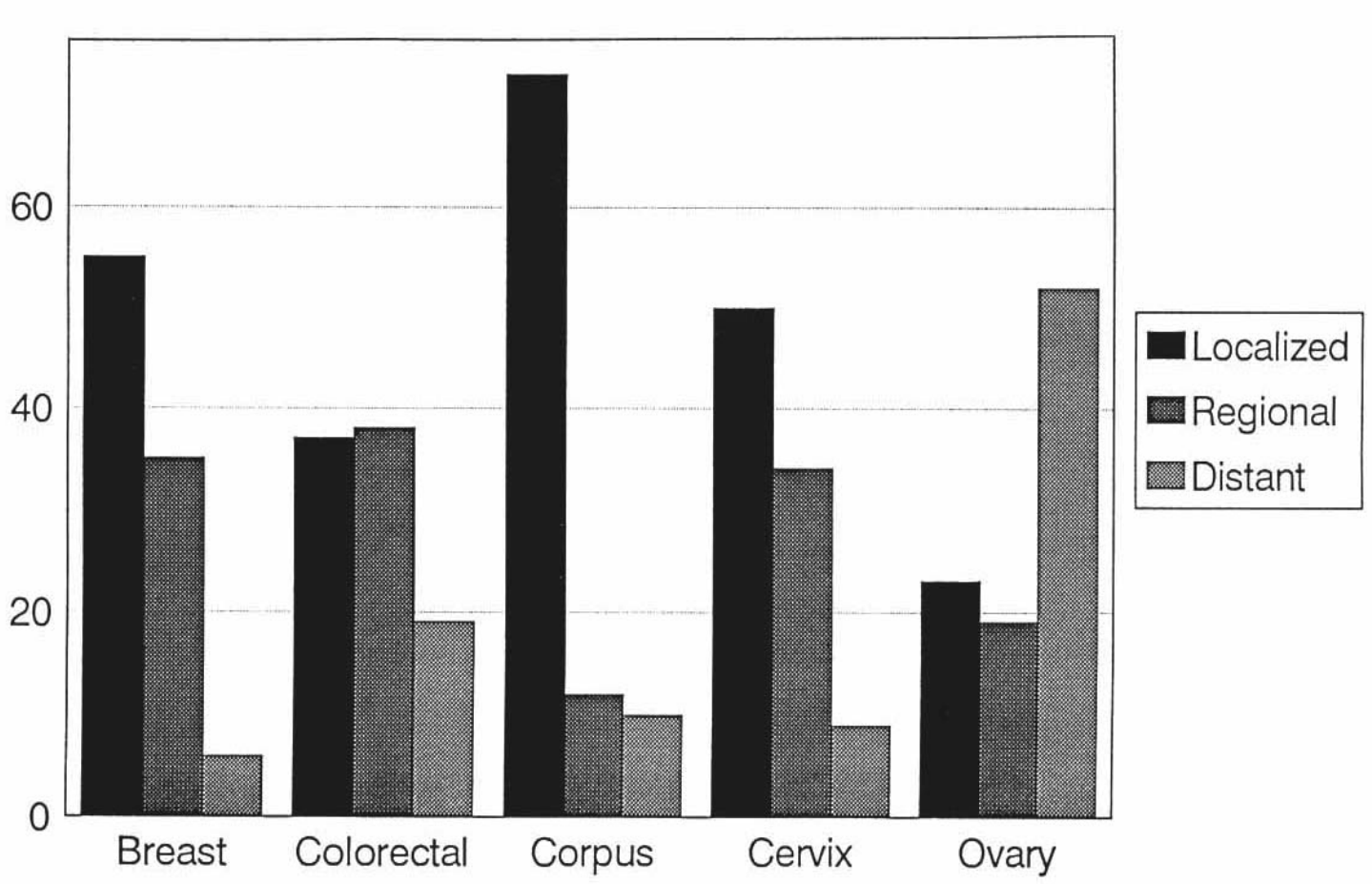


Fig. 5. Percent of new cancer cases by stage at diagnosis for selected cancers: 1983–1990 [1].

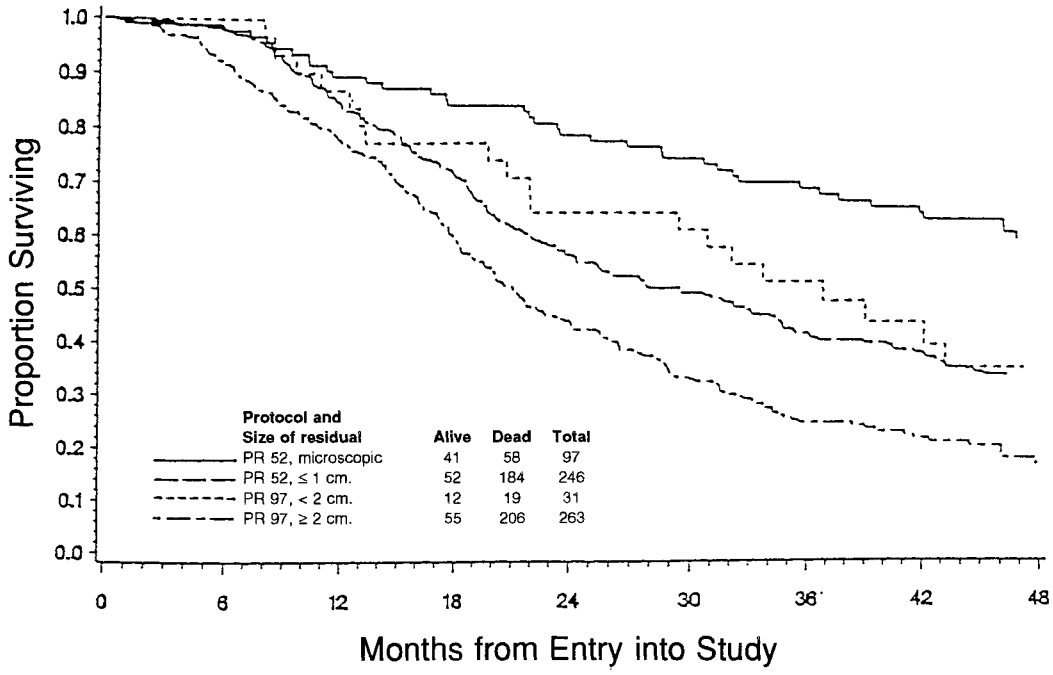


Fig. 6. Survival by residual disease in Gynecologic Oncology Group clinical trials: Protocols #52 and #97.

TABLE IV. Combination Chemotherapy in Advanced Ovarian Cancer: Trials of the Gynecologic Oncology Group [9–12]

Protocol	Overall Response (%)	Complete Response (%)	Pathologic Response (%)	Survival (months)
#47				
Ctx/Adria	47.5	25.8	13.6	16.4
Ctx/Adria/CDDP	75.7	51.4	29.1	19.3
#60				
Ctx/Adra/CDDP +/– BCG*	72.4	48.5	—	22.1
#97				
Ctx/CDDP Standard versus high dose*	62.0	35.5	13.8	20.5
#111				
Ctx/CDDP	64.0	31.0	19.0	24.4
Tx/CDDP	77.0	51.0	26.0	37.5

Ctx = cyclophosphamide; Adria = doxorubicin; CDDP = cisplatin; Tx = paclitaxel.
* In GOG 60 and GOG 97, there was no difference in the two arms, so the two arms are combined and presented as a single total.

TABLE V. Ovarian Cancer—Relative Risk With Oral Contraceptive Use [13]

Duration of Use	Relative Risk	95% CI
Never	1.0	Referent
3–6 months	0.6	0.4–0.9
7–11 months	0.7	0.4–1.3
1–2 years	0.7	0.5–0.9
3–4 years	0.6	0.4–0.9
5–9 years	0.4	0.3–0.6
≥ 10 years	0.2	0.1–0.4

Unfortunately then, the common course of patients with advanced ovarian cancer consists of initial surgery and multi-drug chemotherapy, followed by one or more surgical procedures and one or more salvage chemotherapy regimens. Despite these therapies, most of these patients will eventually present with intestinal obstruction and chemotherapy-resistant disease. Prolonged hospitalization and eventual hospice care are generally the only courses available before the eventual death of the patient.

In summary, the following factors enumerate the problems with ovarian cancer. With no proven premalignant phase of ovarian cancer, we understand little about how the disease develops. Other than listing risk factors, we are unable to document the pathogenesis of the disease or, in most cases, identify those patients who will develop the disease. Early diagnosis occurs infrequently and most patients have a large tumor burden at diagnosis. To date, no screening tests have proven effective. Treatment requires multiple surgical procedures and usually several types of chemotherapy. Despite aggressive therapy with our best agents, the morbidity and mortality are high. The cost of therapy is high both in money and in patient discomfort. Despite the fact that most patients will achieve some type of remission and the median survival is approaching three years, most patients with advanced disease eventually die. Based on the above information, it is clear that ovarian cancer should be targeted for development of preventive measures.

At the current time, there is only one method of preventing ovarian cancer. Using oral contraceptives for over five years has been shown to reduce the incidence of the disease by one-half. Table V shows that use of oral contraceptives for even a year or less results in a substantial incidence reduction [13]. Recent studies have also documented this decrease in risk in women with a family history of ovarian cancer [14]. All women without absolute contraindications for oral contraceptives should be encouraged to take these medications, preferably for at least five years. Fortunately, the incidence of absolute contraindications is rare and significant side effects are low. In the meantime, every effort should be made to improve our understanding of the pathogenesis of the disease so that successful interventions can be developed to prevent its development. Finally, we should develop and test screening tools that will allow early diagnosis for better cure rates.

Ovarian cancer is one of the leading causes of cancer death in women. The treatment of the disease is expensive for society and results in pain and suffering for women. Often, despite aggressive therapy, death is the end result. Both early diagnosis and preventive measures could have a significant impact on the lives of women. There is little doubt about why we should prevent the disease. Every possible effort should be directed towards the development of effective preventive measures.

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