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January 22, 2001

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

CITIZEN PETITION

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. §§ 314.93, 10.20 and 10.30 to request the Commissioner of Food and Drugs to allow the submission of an abbreviated new drug application ("ANDA") for Carboplatin Injection, 10 mg/mL in a ready-to-use solution for injection.

The undersigned also submits this request for a full waiver of pediatric studies for the proposed carboplatin injection product as a primary and secondary treatment for advanced ovarian cancer under 21 C.F.R. § 314.55(c). This waiver is requested because it is impossible or highly impractical to conduct the necessary studies of this drug in a pediatric population due to the extremely small size of the affected population.

A. Action Requested

This petition seeks a determination that the proposed Carboplatin Injection, 10 mg/mL in a ready-to-use solution for injection is suitable for evaluation and approval under an ANDA.

The petition also seeks a full waiver of pediatric studies for this product.

B. Statement of Grounds

1. Suitability Petition

The reference product, Paraplatin® (carboplatin for injection, 50 mg/vial, 150 mg/vial and 450 mg/vial), is a lyophilized powder for reconstitution with Sterile Water for Injection USP, 5% Dextrose in Water or 0.9% Sodium Chloride Injection USP. The proposed product consists of carboplatin already dissolved in Sterile Water for Injection USP. The reference product is

of carboplatin already dissolved in Sterile Water for Injection USP. The reference product is diluted upon reconstitution to a concentration of 10 mg/mL carboplatin. The proposed product as it will be marketed contains 10 mg/mL carboplatin. Additionally, both products contain equal parts by weight of carboplatin and mannitol. Hence, both products have the same active ingredient, route of administration, and strength. The only difference in dosage form between the proposed product and the reference drug is that the proposed product is already dissolved and in a form that is ready for injection, whereas the reference drug is a lyophilized powder for reconstitution. Thus, there is no difference in safety and efficacy between the proposed product and the reference product. The labeling for the proposed product will be identical to that of the reference product, with the exception of the instructions for reconstitution which are not necessary for the proposed product.

Lastly, since the proposed product eliminates the necessity of reconstitution and mixing prior to use, the possibility of improper reconstitution is avoided. The lack of need for reconstitution also minimizes aseptic manipulations of the product, reducing the chance of contamination.

For the above reasons, the petitioner believes that the proposed product is suitable for review under an ANDA, and requests the Commissioner to approve this petition.

2. Request for Full Waiver of Pediatric Studies Requirement

FDA regulations require that "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration" must contain "data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric populations. . . ." 21 C.F.R. § 314.55(a). As this suitability petition requests permission to submit an ANDA for a new dosage form, it may be subject to the pediatric studies requirement. Accordingly, the undersigned hereby requests a full waiver of that requirement for the proposed product under 21 C.F.R. § 314.55(c).

FDA may waive the pediatric study requirements for some or all pediatric age groups if it determines that:

> (i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients,
> (ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or
> (iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

21 C.F.R. § 314.55(c)(2). The undersigned requests this waiver in accordance with § 314.55(c)(2)(ii) because it is impossible or highly impractical to conduct the necessary studies for this drug in a pediatric population due to the affected population's extremely small size.

Paraplatin® for injection (carboplatin) 10 ml, the reference drug for this proposed carboplatin injection drug product, is indicated for primary and secondary treatment of advanced ovarian carcinomas. Ovarian cancer can be divided into two types: germ cell ovarian cancer and non-germ cell ovarian cancer. FDA has included non-germ cell ovarian cancer on a list of diseases that have "extremely limited applicability to pediatric patients" because the disease occurs primarily in the adult population. Draft Guidance for Industry: Recommendations for Complying with the Pediatric Rule (21 C.F.R. § 314.55(a) and 601.27(a)) (Nov. 27, 2000) ("Pediatric Guidance") at 8. FDA has stated that drug products for the treatment of diseases included on this list are likely to be granted a waiver under § 314.55(c). Id. Thus, the undersigned requests a waiver of the pediatric studies requirement for carboplatin injection with respect to non-germ cell ovarian cancer as contemplated in the Pediatric Guidance.

The undersigned also seeks a waiver of pediatric studies with respect to the germ cell ovarian cancer portion of the indication because it is impossible or highly impractical to conduct the necessary studies of this drug in a pediatric population due to the affected population's extremely small size. 21 C.F.R. § 314.55(c)(2)(ii). Unlike most non-germ cell ovarian cancer, ovarian germ cell tumors tend to occur in young women and teenage girls. However, the incidence of ovarian germ cell cancer in girls below the age of 16 in the United States is minuscule -- well under 1,000 -- under a variety of methods for estimating the size of this population.

One way to calculate the pediatric population of ovarian cancer is as a percentage of childhood cancers. Malignant ovarian tumors comprise approximately 1 percent of all cancers in children less than 15 years of age. Lovvorn, et al., "Ovarian Masses in the Pediatric Patient," 67 Ass'n Operating Room Nurses J. 567 (March 1998) (attachment 3). The American Cancer Society ("ACS") expects that 12,400 people under age 20 will be diagnosed with cancer in the year 2000. ACS, Cancer Facts & Figures 2000 at 18 (attachment 4). Thus, under this analysis, ovarian cancer would have affected fewer than 124 pediatric patients in the year 2000.

An alternative way to estimate the incidence of pediatric germ cell ovarian cancer is as a percentage of total ovarian cancer. The ACS estimates that there were approximately 23,100 new cases of ovarian cancer, both germ cell and non-germ cell, diagnosed in the United States in the year 2000. ACS, Cancer Facts & Figures 2000 at 4. Ovarian germ cell cancers account for 2 to 3 percent of all ovarian cancers in Western countries. Cancer: Principles & Practice of Oncology ch. 35.5 (Vincent DeVita, et al., eds. 5th ed. 1997) (attachment 5). Assuming, conservatively, that germ cell ovarian cancer accounts for 3 percent of all ovarian cancer in the United States, approximately 693 new cases of germ cell ovarian cancer are diagnosed each year. However, not all these cases occur in pediatric patients. The peak incidence of germ cell ovarian

cancer occurs in young women in their twenties. Id. Therefore, under this analysis, the number of germ cell ovarian cancer patients in the year 2000 who were under age 16 would be only a fraction of the expected total of 693 such patients.

A third method of estimating the incidence of pediatric ovarian germ cell cancer is to calculate the overall incidence of germ cell tumors as a percentage of childhood cancers. Germ cell tumors as a whole (which include testicular germ cell and central nervous system germ cell cancers as well as germ cell ovarian cancer), along with trophoblastic and other gonadal neoplasms, account for only 3.5 percent of cancer diagnoses in children under age 15, and 7 percent of cancers diagnosed in children and young adults under age 20. ACS, Cancer Facts & Figures 2000 at 21. As noted above, the ACS expects that 12,400 people under age 20 will be diagnosed with cancer in the year 2000. Id. at 18. Under this analysis, germ cell tumors, of which germ cell ovarian tumors are only a portion, would account annually for only 868 cancers in children under 20 and 434 in children under 15.

Yet another estimate of the incidence of ovarian germ cell malignant tumors is 5.3 per million persons under 20. Bernstein, et al., "Germ Cell, Trophoblastic and Other Gonadal Neoplasms," Nat'l Cancer Inst. SEER Pediatric Monograph at 128 (attachment 6). This estimate would yield a total incidence of 434 such tumors in the under-20 population.

Thus, under a variety of methods for estimating the incidence of pediatric germ cell ovarian cancer, the affected population is tiny – well under 1,000. A patient population this small presents practically insurmountable obstacles to clinical research. Even if all the pediatric patients diagnosed with ovarian cancer could somehow be enrolled in a study, the study would probably still have inadequate power to generate meaningful, statistically significant findings. In fact, the approved labeling for the reference listed carboplatin drug notes difficulties in reaching statistical significance due to a limited number of adult patients available for certain portions of the study:

> There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival (≥3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

Reference Product Insert Labeling (attachment).

FDA recently determined that a similarly situated drug, pamidronate disodium injection, was entitled to a full waiver of the requirement to conduct studies in pediatric populations for Paget's Disease and hypercalcemia of malignancy, the drug's approved indications, because of a small or geographically dispersed patient population. See Letter from Gary Buehler, Office of Generic Drugs, to Kala Patel, Faulding Pharmaceutical Co. (Apr. 18, 2000), and Letter from

Heiki Maaser, Faulding Pharmaceutical Co., to FDA (Jan. 14, 2000) (attachment 7). The FDA should likewise find that the pediatric population for advanced ovarian germ cell cancer is too small to practically conduct meaningful studies for carboplatin injection.

For the foregoing reasons, the undersigned requests a full waiver of the pediatric studies requirement for carboplatin injection for the primary and secondary treatment of advanced ovarian cancer in connection with this suitability petition.

C. Environmental Impact

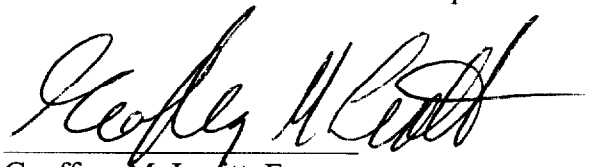
In accord with 21 C.F.R. § 25.31(a), the petitioner claims a categorical exclusion from the requirement to prepare an Environmental Assessment or Environmental Impact Statement since the action requested does not increase the use of the active moiety.

D. Economic Impact

Not applicable.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all the information and views on which the petition relies, and that it includes representative data and information known to the petition which are unfavorable to the petition.



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List of Attachments

1. Paraplatin® (carboplatin for injection) package insert.

2. Proposed Carboplatin Injection Labeling and Comparison with Paraplatin® Labeling.

3. Lovvorn, et al., "Ovarian Masses in the Pediatric Patient," 67 Ass'n Operating Room Nurses J. 567 (March 1998).

4. The American Cancer Society ("ACS") expects that 12,400 people under age 20 will be diagnosed with cancer in the year 2000. ACS, Cancer Facts & Figures 2000.

5. ACS, Cancer Facts & Figures 2000 at 4. Ovarian germ cell cancers account for 2 to 3 percent of all ovarian cancers in Western countries. Cancer: Principles & Practice of Oncology ch. 35.5 (Vincent DeVita, et al., eds. 5th ed. 1997).

6. Bernstein, et al., "Germ Cell, Trophoblastic and Other Gonadal Neoplasms," Nat'l Cancer Inst. SEER Pediatric Monograph.

7. Letter from Gary Buehler, Office of Generic Drugs, to Kala Patel, Faulding Pharmaceutical Co. (Apr. 18, 2000), and Letter from Heiki Maaser, Faulding Pharmaceutical Co., to FDA (Jan. 14, 2000).

8. Paraplatin® (Carboplatin for Injection) Packaging.

9. Proposed Carboplatin Injection Packaging.

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Rx only

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

PARAPLATIN®
(carboplatin for injection)

WARNING

PARAPLATIN (carboplatin for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

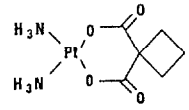
Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to PARAPLATIN have been reported and may occur within minutes of PARAPLATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

PARAPLATIN® (carboplatin for injection) is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato (2-)-O,O'], (SP-4-2), and has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m² of PARAPLATIN. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 - 500 mg/m²).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. PARAPLATIN dosages should therefore be reduced in these patients (see DOSAGE AND ADMINISTRATION).

CLINICAL STUDIES

Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer

In two prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naive patients with advanced ovarian cancer were treated with PARAPLATIN or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. The following results were obtained from both studies:

COMPARATIVE EFFICACY

Overview of Pivotal Trials

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m²	100 mg/m²
Dose of carboplatin	300 mg/m²	300 mg/m²
Dose of CYTOXAN®	600 mg/m²	600 mg/m²
Residual tumor <2 cm (number of patients)	39% (174/447)	14% (49/342)

Clinical Response in Measurable Disease Patients

	NCIC	SWOG
Carboplatin (number of patients)	60% (48/80)	58% (40/83)
Cisplatin (number of patients)	58% (49/85)	43% (33/76)
95% C.I. of difference (Carboplatin – Cisplatin)	(-13.9%, 18.6%)	(-2.3%, 31.1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)

*114 PARAPLATIN and 109 Cisplatin patients did not undergo second look surgery in NCIC study
90 PARAPLATIN and 106 Cisplatin patients did not undergo second look surgery in SWOG study

Progression-Free Survival (PFS)

	NCIC	SWOG
Median		
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin-Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
95% C.I. of difference (Carboplatin-Cisplatin)	(-11.5, 4.5)	(-14.1, 0.3)
Hazard Ratio**	1.10	1.02
95% C.I. (Carboplatin – Cisplatin)	(0.89, 1.35)	(0.81, 1.29)

* Kaplan-Meier Estimates
Unrelated deaths occurring in the absence of progression were counted as events (progression) in this analysis.
** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis

	Survival	
	NCIC	SWOG
Median		
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	75 weeks
2-year Survival*		
Carboplatin	51.9%	40.2%
Cisplatin	48.4%	39.0%
95% C.I. of difference (Carboplatin-Cisplatin)	(-6.2, 13.2)	(-9.8, 12.2)
3-year Survival*		
Carboplatin	34.6%	18.3%
Cisplatin	33.1%	24.9%
95% C.I. of difference (Carboplatin-Cisplatin)	(-7.7, 10.7)	(-15.9, 2.7)
Hazard Ratio**	0.98	1.01
95% C.I. (Carboplatin-Cisplatin)	(0.78, 1.23)	(0.78, 1.30)

* Kaplan-Meier Estimates
** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

COMPARATIVE TOXICITY

The pattern of toxicity exerted by the PARAPLATIN-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care.

The PARAPLATIN-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagic episodes.

Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia, and alopecia) were significantly more frequent in the cisplatin-containing arms.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY

		PARAPLATIN Arm Percent*	cisplatin Arm Percent*	P-Values**
Bone Marrow				
Thrombocytopenia	< 100,000/mm³	70	29	<0.001
	< 50,000 /mm³	41	6	<0.001
Neutropenia	< 2000 cells/mm³	97	96	n.s.
	< 1000 cells/mm³	81	79	n.s.
Leukopenia	< 4000 cells/mm³	98	97	n.s.
	< 2000 cells/mm³	68	52	0.001
Anemia	< 11 g/dL	91	91	n.s.
	< 8 g/dL	18	12	n.s.
Infections		14	12	n.s.
Bleeding		10	4	n.s.
Transfusions		42	31	0.018
Gastrointestinal				
Nausea and vomiting		93	68	0.010
Vomiting		84	97	<0.001
Other GI side effects		50	62	0.013
Neurologic				
Peripheral neuropathies		16	42	<0.001
Ototoxicity		13	33	<0.001
Other sensory side effects		6	10	n.s.
Central neurotoxicity		28	40	0.009
Renal				
Serum creatinine elevations		5	13	0.006
Blood urea elevations		17	31	<0.001
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		17	13	n.s.
Alkaline phosphatase elevations		-	-	-
Electrolytes loss				
Sodium		18	20	0.005
Potassium		16	22	n.s.
Calcium		18	19	n.s.
Magnesium		63	88	<0.001
Other side effects				
Pain		36	37	n.s.
Asthenia		40	33	n.s.
Cardiovascular		15	19	n.s.
Respiratory		8	9	n.s.
Allergic		12	9	n.s.
Genitourinary		10	10	n.s.
Alopecia +		50	62	0.017
Mucositis		10	9	n.s.

* Values are in percent of evaluable patients
** n.s. = not significant, p>0.05
+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY

		PARAPLATIN Arm Percent*	Cisplatin Arm Percent*	P-Values**
Bone Marrow				
Thrombocytopenia	<100,000/mm³	59	35	<0.001
	< 50,000/mm³	22	11	0.006
Neutropenia	< 2000 cells/mm³	95	97	n.s.
	< 1000 cells/mm³	64	78	n.s.
Leukopenia	< 4000 cells/mm³	97	97	n.s.
	< 2000 cells/mm³	75	67	n.s.
Anemia	< 11 g/dL	88	87	n.s.
	< 8 g/dL	6	24	<0.001
Infections		18	21	n.s.
Bleeding		6	4	n.s.
Transfusions		25	33	n.s.
Gastrointestinal				
Nausea and vomiting		94	96	n.s.
Vomiting		82	91	0.007
Other GI side effects		40	48	n.s.
Neurologic				
Peripheral neuropathies		13	28	<0.001
Ototoxicity		12	30	<0.001
Other sensory side effects		4	-	n.s.
Central neurotoxicity		23	29	n.s.
Renal				
Serum creatinine elevations		7	38	<0.001
Blood urea elevations		—	—	-
Hepatic				
Bilirubin elevations		5	3	n.s
SGOT elevations		23	16	n.s.
Alkaline phosphatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
Asthenia		43	46	n.s
Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
Allergic		10	11	n.s.
Genitourinary		11	13	n.s.
Alopecia +		43	57	0.009
Mucositis		6	11	n.s

* Values are in percent of evaluable patients.
** n.s. = not significant, p >0.05
+ May have been affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer

In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy, PARAPLATIN (carboplatin for injection) achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71 + weeks.

INDICATIONS

Initial Treatment of Advanced Ovarian Carcinoma

PARAPLATIN is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of PARAPLATIN and cyclophosphamide (CYTOXAN®). Two randomized controlled studies conducted by the NCIC and SWOG with PARAPLATIN vs. cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see CLINICAL STUDIES section).

There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and long-term survival (≥3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

Secondary Treatment of Advanced Ovarian Carcinoma

PARAPLATIN is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

PARAPLATIN is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.

PARAPLATIN (carboplatin for injection) should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during PARAPLATIN treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent PARAPLATIN. In general, single intermittent courses of PARAPLATIN should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

Since anemia is cumulative, transfusions may be needed during treatment with PARAPLATIN, particularly in patients receiving prolonged therapy.

Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial PARAPLATIN dosages in these patients should be appropriately reduced (see DOSAGE AND ADMINISTRATION) and blood counts should be carefully monitored between courses. The use of PARAPLATIN in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

PARAPLATIN has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when PARAPLATIN was administered at higher than recommended doses in combination with other ototoxic agents.

PARAPLATIN can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of PARAPLATIN, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily pulse doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving PARAPLATIN as secondary treatment.

Loss of vision, which can be complete for light and colors, has been reported after the use of PARAPLATIN with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

As in the case of other platinum coordination compounds, allergic reactions to PARAPLATIN (carboplatin for injection) have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. (See CONTRAINDICATIONS and ADVERSE REACTIONS: Allergic Reactions.)

High dosages of PARAPLATIN (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

PARAPLATIN may cause fetal harm when administered to a pregnant woman. PARAPLATIN has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Needles or intravenous administration sets containing aluminum parts that may come in contact with PARAPLATIN should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Drug Interactions

The renal effects of nephrotoxic compounds may be potentiated by PARAPLATIN.

Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro* and *in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in association with multi-drug therapy.

Pregnancy
Pregnancy Category D: (see WARNINGS).

Nursing Mothers
It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to PARAPLATIN treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with PARAPLATIN (Carboplatin for Injection).

Pediatric Use
Safety and effectiveness in pediatric patients have not been established (see WARNINGS: "audiologic toxicity").

ADVERSE REACTIONS
For a comparison of toxicities when carboplatin or cisplatin was given in combination with cyclophosphamide, see the COMPARATIVE TOXICITY subsection of the CLINICAL STUDIES section.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Bone Marrow			
Thrombocytopenia	< 100,000/mm³	68	82
	< 50,000/mm³	33	35
Neutropenia	< 2000 cells/mm³	96	67
	< 1000 cells/mm³	82	21
Leukopenia	< 4000 cells/mm³	97	85
	< 2000 cells/mm³	71	26
Anemia	< 11 g/dL	90	90
	< 8 g/dL	14	21
Infections		16	5
Bleeding		8	5
Transfusions		35	44
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI side effects		46	21
Neurologic			
Peripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5
Renal			
Serum creatinine elevations		6	10
Blood urea elevations		17	22
Hepatic			
Bilirubin elevations		5	5
SGOT elevations		20	10
Alkaline phosphatase elevations		29	37
Electrolytes less			
Sodium		10	47
Potassium		16	26
Calcium		16	31
Magnesium		61	43
Other side effects			
Pain		44	23
Asthenia		41	11
Cardiovascular		19	6
Respiratory		10	6
Allergic		11	2
Genitourinary		10	2
Alopecia		49	7
Mucositis		8	1

*Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer: Data are based on the experience of 303 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with PARAPLATIN and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see CLINICAL STUDIES section).

Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.

**Single Agent Use for the Secondary Treatment of Ovarian Cancer: Data are based on the experience of 553 patients with previously treated ovarian carcinoma (regardless of baseline status) who received single-agent PARAPLATIN.

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received PARAPLATIN as single-agent therapy.

Hematologic Toxicity
Bone marrow suppression is the dose-limiting toxicity of PARAPLATIN. Thrombocytopenia with platelet counts below 50,000/mm³ occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm³ occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2000/mm³ occurs in 15% of the patients (25% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm³; 74% have neutrophil counts above 2000/mm³; 87% have leukocyte counts above 4000/mm³.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with PARAPLATIN, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to PARAPLATIN. Transfusions have been administered to 26% of the patients treated with PARAPLATIN (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when PARAPLATIN is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity
Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of PARAPLATIN, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule. Emesis was increased when PARAPLATIN was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 5%; and constipation, also in 5%.

Neurologic Toxicity
Peripheral neuropathies have been observed in 4% of the patients receiving PARAPLATIN (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with PARAPLATIN. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

Although the overall incidence of peripheral neurologic side effects induced by PARAPLATIN is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving PARAPLATIN, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during PARAPLATIN therapy.

Hepatic Toxicity
The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of PARAPLATIN and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes
The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 26%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with PARAPLATIN, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions
Hypersensitivity to PARAPLATIN has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance (see WARNINGS). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Other Events
Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely.

Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

OVERDOSAGE
There is no known antidote for PARAPLATIN overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

DOSAGE AND ADMINISTRATION
NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of PARAPLATIN.

Single Agent Therapy
PARAPLATIN (carboplatin for injection), as a single agent, has ..... shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m² IV on day 1 every 4 weeks (Alternatively see Formula Dosing). In general, however, single intermittent courses of PARAPLATIN should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Combination Therapy with Cyclophosphamide
In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:

PARAPLATIN—300 mg/m² IV on day 1 every four weeks for six cycles (Alternatively see Formula Dosing).

Cyclophosphamide (CYTOXAN®)—600 mg/m² IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide (CYTOXAN®) please refer to its package insert. (See CLINICAL STUDIES section.)

Intermittent courses of PARAPLATIN in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations
Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.

The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	Neutrophils	Adjusted Dose * (From Prior Course)
> 100,000	> 2000	125%
50 - 100,000	500 - 2000	No Adjustment
< 50,000	< 500	75%

*Percentages apply to PARAPLATIN (carboplatin for injection) as a single agent or to both PARAPLATIN and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50 to 80%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.

PARAPLATIN is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with Impaired Kidney Function
Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent PARAPLATIN therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

Baseline Creatinine Clearance	Recommended Dose on Day 1
41 - 59 mL/min	250 mg/m²
15 - 40 mL/min	200 mg/m²

The data available for patients with severely impaired kidney function (creatinine clearance below 15 mL/min) are too limited to permit a recommendation for treatment.[1,7]

These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Formula Dosing
Another approach for determining the initial dose of PARAPLATIN is the use of mathematical formulae, which are based on a patient's pre-existing renal function[2-5] or renal function and desired platelet nadir.[6] Renal excretion is the major route of elimination for carboplatin. (See CLINICAL PHARMACOLOGY.) The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).

A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and PARAPLATIN target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert[3-5]. In these studies, GFR was measured by ^{51}Cr-EDTA clearance[7].

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg) = (target AUC) × (GFR + 25)

Note: With the Calvert formula, the total dose of PARAPLATIN is calculated in mg, not mg/m².

The target AUC of 4-6 mg/mL•min using single agent PARAPLATIN appears to provide the most appropriate dose range in previously treated patients[4]. This study also showed a trend between the AUC of single agent PARAPLATIN administered to previously treated patients and the likelihood of developing toxicity[1]:

AUC (mg/mL•min)	% Actual Toxicity in Previously Treated Patients Gr 3 or Gr 4 Thrombocytopenia	Gr 3 or Gr 4 Leukopenia
4 to 5	16%	13%
6 to 7	33%	34%

PREPARATION OF INTRAVENOUS SOLUTIONS
Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D_5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL.

PARAPLATIN can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP.

STABILITY
Unopened vials of PARAPLATIN are stable for the life indicated on the package when stored at controlled room temperature 15°-30° C (59°-86° F), and protected from light.

When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED
PARAPLATIN® (carboplatin for injection)

NDC 0015-3213-30	50 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Yellow flip-off seals)
NDC 0015-3214-30	150 mg vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Violet flip-off seals)
NDC 0015-3215-30	450 mg vials, individually cartoned, shelf packs of 6 cartons, 10 shelf packs per case. (Blue flip-off seals)

STORAGE
Store the unopened vials at controlled room temperature 15°-30° C (59°-86° F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

HANDLING AND DISPOSAL
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published*-**. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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U.S. Patent Nos. 4,140,707
4,657,927

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Revised April 1999

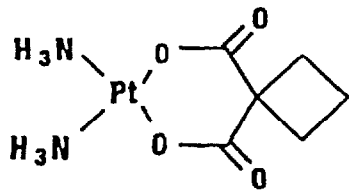
~~PARAPLATIN® (carboplatin for injection)~~Carboplatin Injection 10 mg/ml
Rx only

WARNING

~~PARAPLATIN (carboplatin for injection)~~Carboplatin Injection 10 mg/ml should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy is possible only when adequate treatment facilities are readily available. Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.
Anaphylactic-like reactions to ~~PARAPLATIN~~Carboplatin Injection 10 mg/ml have been reported and may occur within minutes of ~~PARAPLATIN~~Carboplatin Injection administration. Epinephrine , corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

~~PARAPLATIN® (carboplatin for injection)~~Carboplatin Injection 10 mg/ml is supplied as a sterile solution, ~~lyophilized white powder~~ available in single-dose vials containing 50 mg/5 mL, 150 mg/15 mL, and 450 mg/45 mL of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.
Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2), and has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.
In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m^2 of ~~PARAPLATIN~~ carboplatin. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration

vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 – 500 mg/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether bilary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. ~~PARAPLATIN~~Carboplatin dosages should therefore be reduced in these patients (see **DOSAGE AND ADMINISTRATION**).

CLINICAL STUDIES

Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer.

In two prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada, Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naive patients with advanced ovarian cancer were treated with ~~PARAPLATIN~~carboplatin or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. The following results were obtained from both studies:

COMPARATIVE EFFICACY

Overview of Pivotal Trials

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m^2	100 mg/m^2
Dose of carboplatin	300 mg/m^2	300 mg/m^2
Dose of CYTOXAN®	600 mg/m^2	600 mg/m^2
Residual tumor <2 cm (number of patients)	39% (174/447)	14% (49/342)

Clinical Response in Measurable Disease Patients

	NCIC	SWOG
Carboplatin (number of patients)	60% (48/80)	58% (48/83)
Cisplatin (nimber of patients)	58% (49/85)	43% (33/76)
95% C.I. of difference (Carboplatin – Cisplatin)	(-13.9%, 18.6%)	(-2.3%, 31.1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)

* 114 ~~PARAPLATIN~~Carboplatin and 109 Cisplatin patients did not undergo second look surgery in NCIC study.
90 ~~PARAPLATIN~~ Carboplatin and 106 Cisplatin patients did not undergo second look surgery in SWOG study.

Progression-Free Survival (PFS)

Median	**NCIC**	**SWOG**
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin - Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
95% C.I. of difference (Carboplatin - Cisplatin)	(-11.5, 4.5)	(-14.1, 0.3)
Hazard Ratio**	1.10	1.02
95% C.I. (Carboplatin - Cisplatin)	(0.89, 1.35)	(0.81, 1.29)

* Kaplan-Meier Estimates
Unrelated deaths occurring in the absence of progression were counted as events (progression) in this analysis.

** Analysis adjusted for factors found to be of prognostic significance with unadjusted analysis.

Survival

Median	**NCIC**	**SWOG**
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2-year Suvival*		
Carboplatin	51.9%	40.2%
Cisplatin	48,4%	39.0%
95% C.I. of difference (Carboplatin - Cisplatin)	(-6.2, 13.2)	(-9.8, 12.2)
3-year Survival*		
Carboplatin	34.6%	18.3%
Cisplatin	33,1%	24,9%
95% C.I. of difference (Carboplatin - Cisplatin)	(-7.7, 10.7)	(-15.9, 2.7)
Hazard Ratio**	0.98	1.01
95% C.I. (Carboplatin - Cisplatin)	(0.78, 1.23)	(0.78, 1.30)

* Kaplan-Meier Estimates

** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

COMPARATIVE TOXICITY

The pattern of toxicity exerted by the ~~PARAPLATIN~~ Carboplatin-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care.

The ~~PARAPLATIN~~Carboplatin-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagis episodes.

Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia and alopecia) were significantly more frequent in the cisplatin-containing arms.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY				
		PARAPLATIN Arm	CARBOPLATIN Arm	CISPLATIN
Bone Marrow		**Percent***	**Percent***	**P-Values****
Thrombocytopenia	< 100,000/mm^3	70	29	<0.001
	< 50,000/mm^3	41	6	<0.001
Neutropenia	< 2000 cells/mm^3	97	96	n.s.
	< 1000 cells/mm^3	81	79	n.s.
Leukopenia	< 4000 cells/mm^3	98	97	n.s.
	< 2000 cells/mm^3	68	52	0.001
Anemia	< 11 g/dL	91	91	n.s.
	< 8 g/dL	18	12	n.s.
Infections		14	12	n.s.
Bleeding		10	4	n.s.
Transfusions		42	31	0.018
Gastrointestinal				
Nausea and vomiting		93	98	0.010
Vomiting		84	97	<0.001
Other GI side effects		50	62	0.013
Neurologic				
Pheripheral neuropathies		16	42	<0.001
Ototoxicity		13	33	<0.001
Other sensory side effects		6	10	n.s.
Central neurotoxicity		28	40	0.009
Renal				
Serum creatinine elevations		5	13	0.006
Blood urea elevations		17	31	<0.001
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		17	13	n.s.
Alkaline phosphatase elevations		-	-	-
Electrolytes loss				
Sodium		10	20	0.005
Potassium		16	22	n.s.
Calcium		16	19	n.s.
Magnesium		63	88	<0.001
Other side effects				
Pain		36	37	n.s.
Asthenia		40	33	n.s.
Cardiovascular		15	19	n.s.
Respiratory		8	9	n.s.
Allergic		12	9	n.s.
Genitourinary		10	10	n.s.
Alopecia +		50	62	0.017
Mucositis		10	9	n.s.

* Values are in percent of evaluable patients

** n.s. = not significant, p>0.05

\+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		~~PARAPLATIN~~CARBOPLATIN		CISPLATIN
Bone Marrow		**Arm Percent***	**Arm Percent***	**P-Values****
Trombocytopenia	< 100,000/mm^3	59	35	<0.001
	< 50,000/mm^3	22	11	0.006
Neutropenia	< 2000 cells/mm^3	95	97	n.s.
	< 1000 cells/mm^3	84	78	n.s.
Leukopenia	< 4000 cells/mm^3	97	97	n.s.
	< 2000 cells/mm^3	76	67	n.s.
Anemia	< 11 g/dL	88	87	n.s.
	< 8 g/dL	8	24	<0.001
Infections		18	21	n.s.
Bleeding		6	4	n.s.
Transfusion		25	33	n.s.
Gastrointestinal				
Nausea and vomiting		94	96	n.s.
Vomiting		82	91	0.007
Other GI side effects		40	48	n.s.
Neurologic				
Pheripheral neuropathies		13	28	0.001
Ototoxicity		12	30	<0.001
Other sensory side effects		4	6	n.s.
Central neurotoxicity		23	29	n.s.
Renal				
Serum creatinine elevations		7	38	<0.001
Blood urea elevations		-	-	-
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		23	16	n.s.
Alkaline phophatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
Asthenia		43	46	n.s.
Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
Allergic		10	11	n.s.
Genitourinary		11	13	n.s.
Alopecia +		43	57	0.009
Mucositis		6	11	n.s.

* Values are in percent of evaluable patients

** n.s. = not significant, p>0.05

\+ May have been affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer
In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy, ~~PARAPLATIN (carboplatin for injection)~~Carboplatin achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71 + weeks.

INDICATIONS

Initial Treatment of Advanced Ovarian Carcinoma
~~PARAPLATIN~~Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of ~~PARAPLATIN~~carboplatin and cyclophosphamide (CYTOXAN ®). Two randomized controlled studies conducted by the NCIC and SWOG with ~~PARAPLATIN~~carboplatin vs. cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see **CLINICAL STUDIES** section).
There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival (≥3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

Secondary Treatment of Advanced Ovarian Carcinoma
~~PARAPLATIN~~Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.
Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

~~PARAPLATIN~~Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.
~~PARAPLATIN (carboplatin for injection)~~Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during ~~PARAPLATIN~~carboplatin treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent ~~PARAPLATIN~~carboplatin. In general, single intermittent courses of ~~PARAPLATIN~~carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.
Since anemia is cumulative, transfusions may be needed during treatment with ~~PARAPLATIN~~carboplatin, particularly in patients receiving prolonged therapy.
Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial ~~PARAPLATIN~~carboplatin dosages in these patients should be appropriately reduced (see **DOSAGE AND ADMINISTRATION**) and blood counts should be carefully monitored between courses.
The use of ~~PARAPLATIN~~carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

~~PARAPLATIN~~Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when ~~PARAPLATIN~~carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

~~PARAPLATIN~~Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of ~~PARAPLATIN~~carboplatin, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily pulse doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving ~~PARAPLATIN~~carboplatin as secondary treatment.

Loss of vision, which can be complete for light and colors, has been reported after the use of ~~PARAPLATIN~~carboplatin with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

As in the case of other platinum coordination compounds allergic reactions to ~~PARAPLATIN (carboplatin for injection)~~carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS: Allergic Reactions.**)

High dosages of ~~PARAPLATIN~~carboplatin (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

~~PARAPLATIN~~Carboplatin may cause fetal harm when administered to a pregnant woman. ~~PARAPLATIN~~Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Needles or intravenous administration sets containing aluminum parts that may come in contact with ~~PARAPLATIN~~carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Drug Interactions

The renal effects of nephrotoxic compounds may be potentiated by ~~PARAPLATIN~~carboplatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro* and *in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in assocciation with multi-drug therapy.

Pregnancy

Pregnancy Category D: (see **WARNINGS).**

Nursing Mothers
It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to ~~PARAPLATIN~~carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with ~~PARAPLATIN (carboplatin for injection)~~carboplatin.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established (see **WARNINGS;** "audiologic toxicity").

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin was given in combination with cyclophosphamide, see the **COMPARATIVE TOXICITY** subsection of the **CLINICAL STUDIES** section.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Bone Marrow			
Thrombocytopenia	< 100,000/mm^3	66	62
	< 50,000/mm^3	33	35
Neutropenia	< 2000 cells/mm^3	96	67
	< 1000 cells/mm^3	82	21
Leukopenia	< 4000 cells/mm^3	97	85
	< 2000 cells/mm^3	71	26
Anemia	< 11 g/dL	90	90
	< 8 g/dL	14	21
Infections		16	5
Bleeding		8	5
Transfusions		35	44
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI ide effects		46	21
Neurologic			
Pheripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5
Renal			
Serum creatinine elevations		6	10
Blood urea elevations		17	22
Hepatic			
Bilirubin elevations		5	5
SGOT elevations		20	19
Alkaline phosphatase elevations		29	37
Electrolytes loss			
Sodium		10	47
Potassium		16	28
Calcium		16	31
Magnesium		61	43
Other side effects			
Pain		44	23
Asthenia		41	11
Cardiovascular		19	6
Respiratory		10	6
Allergic		11	2
Genitourinary		10	2
Alopecia		49	2
Mucositis		8	1

* **Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer:** Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with ~~PARAPLATIN~~carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see **CLINICAL STUDIES** section).
Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.

** **Single Agent Use for the Secondary Treatment of Ovarian Cancer:** Data are based on the experience of 553 patients with previously treated ovaian carcinoma (regardless of baseline status) who received single-agent ~~PARAPLATIN~~carboplatin.

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received ~~PARAPLATIN~~carboplatin as single-agent therapy.

Hematologic Toxicity

Bone marrow suppression is the dose-limiting toxicity of ~~PARAPLATIN~~carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm^3 occurs in 16% of the patients (21% of pretreated overian cancer patients); leukopenia with WBC counts below 2000/mm^3 occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2000/mm^3, 67% have leukocyte counts above 4000/mm^3.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with ~~PARAPLATIN~~carboplatin, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia. Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to ~~PARAPLATIN~~carboplatin. Transfusions have been administered to 26% of the patients treated with ~~PARAPLATIN~~carboplatin (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when ~~PARAPLATIN~~carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity

Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of ~~PARAPLATIN~~carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule. Emesis was increased when ~~PARAPLATIN~~carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6% and constipation, also in 6%.

Neurologic Toxicity
Peripheral neuropathies have been observed in 4% of the patients receiving ~~PARAPLATIN~~carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with ~~PARAPLATIN~~carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.
Although the overall incidence of peripheral neurologic side effects induced by ~~PARAPLATIN~~carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about on-half of them were reversible. Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving ~~PARAPLATIN~~carboplatin, and appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during ~~PARAPLATIN~~carboplatin therapy.

Hepatic Toxicity
The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of ~~PARAPLATIN~~carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes
The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with ~~PARAPLATIN~~carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions
Hypersensitivity to ~~PARAPLATIN~~carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing- surveillance (see **WARNINGS**). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Other Events
Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cadiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely. Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

OVERDOSAGE
There is no known antidote for ~~PARAPLATIN~~carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

DOSAGE AND ADMINISTRATION
NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of ~~PARAPLATIN~~carboplatin.

Singel Agent Therapy
~~PARAPLATIN (carboplatin for injection)~~Carboplatin, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m² IV on day 1 every 4 weeks (Alternatively see **Formula Dosing**). In general, however, single intermittent courses of ~~PARAPLATIN~~carboplatin should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Combination Therapy with Cyclophosphamide
In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:
~~PARAPLATIN~~-Carboplatin 300 mg/m² IV on day 1 every four weeks for six cycles (Alternatively see **Formula Dosing**) .
Cyclophosphamide (CYTOXAN®)-600 mg/m² IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide (CYTOXAN®) please refer to its package insert. (See **CLINICAL STUDIES** section.)
Intermittent courses of ~~PARAPLATIN~~carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations
Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.
The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	**Neutrophils**	**Adjusted Dose* (From Prior Course)**
> 100,000	> 2000	125%
50 – 100,000	500 – 2000	No Adjustment
< 50,000	< 500	75%

* Percentages apply to ~~PARAPLATIN (carboplatin for injection)~~carboplatin as a single agent or to both ~~PARAPLATIN~~carboplatin and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50 to 60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies.
~~PARAPLATIN~~Carboplatin is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with Impaired Kidney Function
Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent ~~PARAPLATIN~~carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

Baseline Creatinine Clearance	Recommended Dose on Day 1
41 – 59 mL/min	250 mg/m²
16 – 40 mL/min	200 mg/m²

The data available for patients with severely impaired kidney function (creatinine clearance below 15mL/min) are too limited to permit a recommendation for treatment. [1,2]
These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Formula Dosing
Another approach for determining the initial dose of ~~PARAPLATIN~~carboplatin is the use of mathematical formulae, which are based on a patient's pre-existing renal function[3-5] or renal function and desired platelet nadir.[6] Renal excretion is the major route of elimination for carboplatin. (See **CLINICAL PHARMACOLOGY.**) The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).
A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and ~~PARAPLATIN~~carboplatin target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert[3-5]. In these studies, GFR was measured by ^{51}Cr-EDTA clearance[7].

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg)=(target AUC) x (GFR + 25)

Note: With the Calvert formula, the total dose of ~~PARAPLATIN~~carboplatin is calculated in mg, not mg/m².

The target AUC of 4-6 mg/mL•min using single agent ~~PARAPLATIN~~carboplatin appears to provide the most appropriate dose range in previously treated patients[4]. This study also showed a trend between the AUC of single agent ~~PARAPLATIN~~carboplatin administered to previously treated patients and the likelihood of developing toxicity[1].

AUC (mg/mL•min)	% Actual Toxicity in Previously Treated Patients GR 3 or Gr 4 Trombocytopenia	Gr 3 or Gr 4 Leukopenia
4 to 5	16%	13%
6 to 7	33%	34%

~~PREPARATION OF INTRAVENOUS SOLUTIONS~~

~~Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, USP, 5% Dextrose in Water (D_5W), or 0.9% Sodium Chloride Injection, USP, according to the following schedule:~~

~~Vial Strength~~	~~Diluent Volume~~
~~50 mg~~	~~5 mL~~
~~150 mg~~	~~15 mL~~
~~450 mg~~	~~45 mL~~

~~These dilutions all produce a carboplatin concentration of 10 mg/mL.~~

PREPARATION OF DILUTED SOLUTION FOR INJECTION

~~PARAPLATIN~~Carboplatin injection 10 mg/mL can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP.

STABILITY

Unopened vials of ~~PARAPLATIN~~carboplatin injection are stable for the life indicated on the package when stored at controlled room temperature 15°-~~30~~25° C (~~59°-86° F~~), and protected from light.

~~When prepared as directed, PARAPLATIN solutions are stable for 8 hours at room temperature (25° C). Since no antibacterial preservative is contained in the formulation, it is recommended that PARAPLATIN solutions be discarded 8 hours after dilution.~~

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

~~PARAPLATIN® (carboplatin for injection)~~

~~**NDC** 0015-3213-30 **50 mg** vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Yellow flip-off seals)~~

~~**NDC** 0015-3214-30 **150 mg** vials, individually cartoned, shelf packs of 10 cartons, 10 shelf packs per case. (Violet flip-off seals)~~

~~**NDC** 0015-3215-30 **450 mg** vials, individually cartoned, shelf packs of 6 cartons, 10 shelf packs per case. (Blue flip-off seals)~~

Carboplatin injection 10 mg/mL is available in vials containing 5 mL, 15 mL and 45 mL.

STORAGE

Store the unopened vials at controlled room temperature 15°-~~30~~25° C (~~59° 86° F~~). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published[8-14]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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U.S. Patent Nos. 4, 140,707
4, 657,927

Carboplatin Injection 10 mg/ml **Rx only**

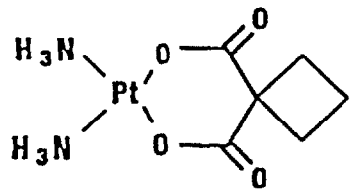
WARNING

Carboplatin Injection 10 mg/mlshould be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy is possible only when adequate treatment facilities are readily available. Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to Carboplatin Injection 10 mg/ml have been reported and may occur within minutes of Carboplatin Injection administration. Epinephrine , corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

Carboplatin Injection 10 mg/ml is supplied as a sterile solution, available in single-dose vials containing 50 mg/5 mL, 150 mg/15 mL, and 450 mg/45 mL of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol. Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2), and has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of $C_{16}H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5-7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

CLINICAL PHARMACOLOGY

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m^2 of carboplatin. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, and 3.5 hours, respectively. The C_{max} values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly

more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 – 500 mg/m^2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether bilary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances of carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients (see **DOSAGE AND ADMINISTRATION**).

CLINICAL STUDIES

Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer.

In two prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada, Clinical Trials Group (NCIC) and the Southwest Oncology Group (SWOG), 789 chemotherapy naive patients with advanced ovarian cancer were treated with carboplatin or cisplatin, both in combination with cyclophosphamide every 28 days for six courses before surgical reevaluation. The following results were obtained from both studies:

COMPARATIVE EFFICACY

Overview of Pivotal Trials

	NCIC	SWOG
Number of patients randomized	447	342
Median age (years)	60	62
Dose of cisplatin	75 mg/m^2	100 mg/m^2
Dose of carboplatin	300 mg/m^2	300 mg/m^2
Dose of CYTOXAN®	600 mg/m^2	600 mg/m^2
Residual tumor <2 cm (number of patients)	39% (174/447)	14% (49/342)

Clinical Response in Measurable Disease Patients

	NCIC	SWOG
Carboplatin (number of patients)	60% (48/80)	58% (48/83)
Cisplatin (nimber of patients)	58% (49/85)	43% (33/76)
95% C.I. of difference (Carboplatin – Cisplatin)	(-13.9%, 18.6%)	(-2.3%, 31.1%)

Pathologic Complete Response*

	NCIC	SWOG
Carboplatin (number of patients)	11% (24/224)	10% (17/171)
Cisplatin (number of patients)	15% (33/223)	10% (17/171)
95% C.I. of difference (Carboplatin – Cisplatin)	(-10.7%, 2.5%)	(-6.9%, 6.9%)

* 114 Carboplatin and 109 Cisplatin patients did not undergo second look surgery in NCIC study. 90 PARAPLATIN and 106 Cisplatin patients did not undergo second look surgery in SWOG study.

Progression-Free Survival (PFS)

Median	**NCIC**	**SWOG**
Carboplatin	59 weeks	49 weeks
Cisplatin	61 weeks	47 weeks
2-year PFS*		
Carboplatin	31%	21%
Cisplatin	31%	21%
95% C.I. of difference (Carboplatin - Cisplatin)	(-9.3, 8.7)	(-9.0, 9.4)
3-year PFS*		
Carboplatin	19%	8%
Cisplatin	23%	14%
95% C.I. of difference (Carboplatin - Cisplatin)	(-11.5, 4.5)	(-14.1, 0.3)
Hazard Ratio**	1.10	1.02
95% C.I. (Carboplatin - Cisplatin)	(0.89, 1.35)	(0.81, 1.29)

* Kaplan-Meier Estimates
Unrelated deaths occurring in the absence of progression were counted as events (progression) in this analysis.

** Analysis adjusted for factors found to be of prognostic significance with unadjusted analysis.

Survival

Median	**NCIC**	**SWOG**
Carboplatin	110 weeks	86 weeks
Cisplatin	99 weeks	79 weeks
2-year Suvival*		
Carboplatin	51.9%	40.2%
Cisplatin	48,4%	39.0%
95% C.I. of difference (Carboplatin - Cisplatin)	(-6.2, 13.2)	(-9.8, 12.2)
3-year Survival*		
Carboplatin	34.6%	18.3%
Cisplatin	33,1%	24,9%
95% C.I. of difference (Carboplatin - Cisplatin)	(-7.7, 10.7)	(-15.9, 2.7)
Hazard Ratio**	0.98	1.01
95% C.I. (Carboplatin - Cisplatin)	(0.78, 1.23)	(0.78, 1.30)

* Kaplan-Meier Estimates

** Analysis adjusted for factors found to be of prognostic significance were consistent with unadjusted analysis.

COMPARATIVE TOXICITY

The pattern of toxicity exerted by the PARAPLATIN-containing regimen was significantly different from that of the cisplatin-containing combinations. Differences between the two studies may be explained by different cisplatin dosages and by different supportive care.

The PARAPLATIN-containing regimen induced significantly more thrombocytopenia and, in one study, significantly more leukopenia and more need for transfusional support. The cisplatin-containing regimen produced significantly more anemia in one study. However, no significant differences occurred in incidences of infections and hemorrhagis episodes.

Non-hematologic toxicities (emesis, neurotoxicity, ototoxicity, renal toxicity, hypomagnesemia and alopecia) were significantly more frequent in the cisplatin-containing arms.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER NCIC STUDY				
		CARBOPLATIN Arm Percent*	CISPLATIN Arm Percent*	P-Values**
Bone Marrow				
Trombocytopenia	< 100,000/mm^3	70	29	<0.001
	< 50,000/mm^3	41	6	<0.001
Neutropenia	< 2000 cells/mm^3	97	96	n.s.
	< 1000 cells/mm^3	81	79	n.s.
Leukopenia	< 4000 cells/mm^3	98	97	n.s.
	< 2000 cells/mm^3	68	52	0.001
Anemia	< 11 g/dL	91	91	n.s.
	< 8 g/dL	18	12	n.s.
Infections		14	12	n.s.
Bleeding		10	4	n.s.
Transfusions		42	31	0.018
Gastrointestinal				
Nausea and vomiting		93	98	0.010
Vomiting		84	97	<0.001
Other GI side effects		50	62	0.013
Neurologic				
Pheripheral neuropathies		16	42	<0.001
Ototoxicity		13	33	<0.001
Other sensory side effects		6	10	n.s.
Central neurotoxicity		28	40	0.009
Renal				
Serum creatinine elevations		5	13	0.006
Blood urea elevations		17	31	<0.001
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		17	13	n.s.
Alkaline phophatase elevations		-	-	-
Electrolytes loss				
Sodium		10	20	0.005
Potassium		16	22	n.s.
Calcium		16	19	n.s.
Magnesium		63	88	<0.001
Other side effects				
Pain		36	37	n.s.
Asthenia		40	33	n.s.
Cardiovascular		15	19	n.s.
Respiratory		8	9	n.s.
Allergic		12	9	n.s.
Genitourinary		10	10	n.s.
Alopecia +		50	62	0.017
Mucositis		10	9	n.s.

* Values are in percent of evaluable patients

** n.s. = not significant, p>0.05

\+ May have been affected by cyclophosphamide dosage delivered

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER SWOG STUDY				
		CARBOPLATIN Arm	CISPLATIN Arm	
Bone Marrow		**Percent***	**Percent***	**P-Values****
Trombocytopenia	< 100,000/mm^3	59	35	<0.001
	< 50,000/mm^3	22	11	0.006
Neutropenia	< 2000 cells/mm^3	95	97	n.s.
	< 1000 cells/mm^3	84	78	n.s.
Leukopenia	< 4000 cells/mm^3	97	97	n.s.
	< 2000 cells/mm^3	76	67	n.s.
Anemia	< 11 g/dL	88	87	n.s.
	< 8 g/dL	8	24	<0.001
Infections		18	21	n.s.
Bleeding		6	4	n.s.
Transfusion		25	33	n.s.
Gastrointestinal				
Nausea and vomiting		94	96	n.s.
Vomiting		82	91	0.007
Other GI side effects		40	48	n.s.
Neurologic				
Pheripheral neuropathies		13	28	0.001
Ototoxicity		12	30	<0.001
Other sensory side effects		4	6	n.s.
Central neurotoxicity		23	29	n.s.
Renal				
Serum creatinine elevations		7	38	<0.001
Blood urea elevations		-	-	-
Hepatic				
Bilirubin elevations		5	3	n.s.
SGOT elevations		23	16	n.s.
Alkaline phophatase elevations		29	20	n.s.
Electrolytes loss				
Sodium		-	-	-
Potassium		-	-	-
Calcium		-	-	-
Magnesium		58	77	<0.001
Other side effects				
Pain		54	52	n.s.
Asthenia		43	46	n.s.
Cardiovascular		23	30	n.s.
Respiratory		12	11	n.s.
Allergic		10	11	n.s.
Genitourinary		11	13	n.s.
Alopecia +		43	57	0.009
Mucositis		6	11	n.s.

* Values are in percent of evaluable patients

** n.s. = not significant, $p>0.05$

\+ May have been affected by cyclophosphamide dosage delivered

Use as a Single Agent for Secondary Treatment of Advanced Ovarian Cancer
In two prospective, randomized controlled studies in patients with advanced ovarian cancer previously treated with chemotherapy, Carboplatin achieved six clinical complete responses in 47 patients. The duration of these responses ranged from 45 to 71 + weeks.

INDICATIONS

Initial Treatment of Advanced Ovarian Carcinoma
Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents. One established combination regimen consists of carboplatin and cyclophosphamide (CYTOXAN ®). Two randomized controlled studies conducted by the NCIC and SWOG with carboplatin vs. cisplatin, both in combination with cyclophosphamide, have demonstrated equivalent overall survival between the two groups (see **CLINICAL STUDIES** section).
There is limited statistical power to demonstrate equivalence in overall pathologic complete response rates and longterm survival (≥3 years) because of the small number of patients with these outcomes: the small number of patients with residual tumor <2 cm after initial surgery also limits the statistical power to demonstrate equivalence in this subgroup.

Secondary Treatment of Advanced Ovarian Carcinoma
Carboplatin is indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin. Within the group of patients previously treated with cisplatin, those who have developed progressive disease while receiving cisplatin therapy may have a decreased response rate.

CONTRAINDICATIONS

Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds, or mannitol.
Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

WARNINGS

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent carboplatin. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered. Since anemia is cumulative, transfusions may be needed during treatment with carboplatin, particularly in patients receiving prolonged therapy.
Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced (see **DOSAGE AND ADMINISTRATION**) and blood counts should be carefully monitored between courses.
The use of carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.
Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric

patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.
Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of carboplatin, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily pulse doses has resulted in reduced emesis.
Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving carboplatin as secondary treatment.
Loss of vision, which can be complete for light and colors, has been reported after the use of carboplatin with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.
As in the case of other platinum coordination compounds allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy. (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS: Allergic Reactions.)**
High dosages of carboplatin (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.
Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Drug Interactions

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both *in vitro* and *in vivo*. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in assocciation with multi-drug therapy.

Pregnancy

Pregnancy Category D: (see **WARNINGS).**

Nursing Mothers

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with carboplatin.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established (see **WARNINGS;** "audiologic toxicity").

ADVERSE REACTIONS

For a comparison of toxicities when carboplatin was given in combination with cyclophosphamide, see the **COMPARATIVE TOXICITY** subsection of the **CLINICAL STUDIES** section.

ADVERSE EXPERIENCES IN PATIENTS WITH OVARIAN CANCER

		First Line Combination Therapy* Percent	Second Line Single Agent Therapy** Percent
Bone Marrow			
Trombocytopenia	< 100,000/mm^3	66	62
	< 50,000/mm^3	33	35
Neutropenia	< 2000 cells/mm^3	96	67
	< 1000 cells/mm^3	82	21
Leukopenia	< 4000 cells/mm^3	97	85
	< 2000 cells/mm^3	71	26
Anemia	< 11 g/dL	90	90
	< 8 g/dL	14	21
Infections		16	5
Bleeding		8	5
Transfusions		35	44
Gastrointestinal			
Nausea and vomiting		93	92
Vomiting		83	81
Other GI ide effects		46	21
Neurologic			
Pheripheral neuropathies		15	6
Ototoxicity		12	1
Other sensory side effects		5	1
Central neurotoxicity		26	5
Renal			
Serum creatinine elevations		6	10
Blood urea elevations		17	22
Hepatic			
Bilirubin elevations		5	5
SGOT elevations		20	19
Alkaline phosphatase elevations		29	37
Electrolytes loss			
Sodium		10	47
Potassium		16	28
Calcium		16	31
Magnesium		61	43
Other side effects			
Pain		44	23
Asthenia		41	11
Cardiovascular		19	6
Respiratory		10	6
Allergic		11	2
Genitourinary		10	2
Alopecia		49	2
Mucositis		8	1

* **Use with Cyclophosphamide for Initial Treatment of Ovarian Cancer:** Data are based on the experience of 393 patients with ovarian cancer (regardless of baseline status) who received initial combination therapy with carboplatin and cyclophosphamide in two randomized controlled studies conducted by SWOG and NCIC (see **CLINICAL STUDIES** section). Combination with cyclophosphamide as well as duration of treatment may be responsible for the differences that can be noted in the adverse experience table.
** **Single Agent Use for the Secondary Treatment of Ovarian Cancer:** Data are based on the experience of 553 patients with previously treated ovaian carcinoma (regardless of baseline status) who received single-agent carboplatin.

In the narrative section that follows, the incidences of adverse events are based on data from 1893 patients with various types of tumors who received carboplatin as single-agent therapy.

Hematologic Toxicity

Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm^3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm^3 occurs in 16% of the patients (21% of pretreated overian cancer patients); leukopenia with WBC counts below 2000/mm^3 occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm^3; 74% have neutrophil counts above 2000/mm^3, 67% have leukocyte counts above 4000/mm^3.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.

The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with carboplatin, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity

Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients. Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule. Emesis was increased when carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6% and constipation, also in 6%.

Neurologic Toxicity
Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.
Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity
Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about on-half of them were reversible. Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during carboplatin therapy.

Hepatic Toxicity
The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%, 19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes
The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions
Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, ie, rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance (see **WARNINGS**). These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Other Events

Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia was likely. Alopecia was reported (3%). Cadiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely. Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

OVERDOSAGE

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

DOSAGE AND ADMINISTRATION

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Singel Agent Therapy

Carboplatin, as a single agent, has been shown to be effective in patients with recurrent ovarian carcinoma at a dosage of 360 mg/m² IV on day 1 every 4 weeks (Alternatively see **Formula Dosing**). In general, however, single intermittent courses of carboplatin should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Combination Therapy with Cyclophosphamide

In the chemotherapy of advanced ovarian cancer, an effective combination for previously untreated patients consists of:
-300 mg/m² IV on day 1 every four weeks for six cycles (Alternatively see **Formula Dosing**) .
Cyclophosphamide (CYTOXAN®)-600 mg/m² IV on day 1 every four weeks for six cycles. For directions regarding the use and administration of cyclophosphamide (CYTOXAN®) please refer to its package insert. (See **CLINICAL STUDIES** section.)
Intermittent courses of carboplatin in combination with cyclophosphamide should not be repeated until the neutrophil count is at least 2000 and the platelet count is at least 100,000.

Dose Adjustment Recommendations

Pretreatment platelet count and performance status are important prognostic factors for severity of myelosuppression in previously treated patients.
The suggested dose adjustments for single agent or combination therapy shown in the table below are modified from controlled trials in previously treated and untreated patients with ovarian carcinoma. Blood counts were done weekly, and the recommendations are based on the lowest post-treatment platelet or neutrophil value.

Platelets	**Neutrophils**	**Adjusted Dose* (From Prior Course)**
> 100,000	> 2000	125%
50 – 100,000	500 – 2000	No Adjustment
< 50,000	< 500	75%

* Percentages apply to carboplatin as a single agent or to both carboplatin and cyclophosphamide in combination. In the controlled studies, dosages were also adjusted at a lower level (50 to 60%) for severe myelosuppression. Escalations above 125% were not recommended for these studies. Carboplatin is usually administered by an infusion lasting 15 minutes or longer. No pre- or post-treatment hydration or forced diuresis is required.

Patients with Impaired Kidney Function
Patients with creatinine clearance values below 60 mL/min are at increased risk of severe bone marrow suppression. In renally-impaired patients who received single agent carboplatin therapy, the incidence of severe leukopenia, neutropenia, or thrombocytopenia has been about 25% when the dosage modifications in the table below have been used.

Baseline Creatinine Clearance	Recommended Dose on Day 1
41 – 59 mL/min	250 mg/m²
16 – 40 mL/min	200 mg/m²

The data available for patients with severely impaired kidney function (creatinine clearance below 15mL/min) are too limited to permit a recommendation for treatment. [1,2]
These dosing recommendations apply to the initial course of treatment. Subsequent dosages should be adjusted according to the patient's tolerance based on the degree of bone marrow suppression.

Formula Dosing
Another approach for determining the initial dose of carboplatin is the use of mathematical formulae, which are based on a patient's pre-existing renal function[3-5] or renal function and desired platelet nadir.[6] Renal excretion is the major route of elimination for carboplatin. (See **CLINICAL PHARMACOLOGY.**) The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).
A simple formula for calculating dosage, based upon a patient's glomerular filtration rate (GFR in mL/min) and carboplatin target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert[3-5]. In these studies, GFR was measured by ^{51}Cr-EDTA clearance[7].

CALVERT FORMULA FOR CARBOPLATIN DOSING

Total Dose (mg)=(target AUC) x (GFR + 25)

Note: With the Calvert formula, the total dose of carboplatin is calculated in mg, not mg/m².

The target AUC of 4-6 mg/mL•min using single agent carboplatin appears to provide the most appropriate dose range in previously treated patients[4]. This study also showed a trend between the AUC of single agent carboplatin administered to previously treated patients and the likelihood of developing toxicity[1].

AUC (mg/mL•min)	% Actual Toxicity in Previously Treated Patients GR 3 or Gr 4 Trombocytopenia	 Gr 3 or Gr 4 Leukopenia
4 to 5	16%	13%
6 to 7	33%	34%

PREPARATION OF DILUTED SOLUTION FOR INJECTION
Carboplatin injection 10 mg/mL can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D_5W) or 0.9% Sodium Chloride Injection, USP.

STABILITY
Unopened vials of carboplatin injection are stable for the life indicated on the package when stored at controlled room temperature 15°-25° C , and protected from light.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED
Carboplatin injection 10 mg/mL is available in vials containing 5 mL, 15 mL and 45 mL.

STORAGE
Store the unopened vials at controlled room temperature 15°-25° C . Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.
HANDLING AND DISPOSAL
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published[8-14]. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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BYLINE: Lovvorn, Harold N., III; Tucci, Lisa Ann; Stafford, Perry W.

AUTHOR-ABSTRACT:
Ovarian masses in the pediatric patient are uncommon. Children with ovarian tumors, however, pose diagnostic and therapeutic challenges because their presentation can mimic other more common intraabdominal disorders and their tumor histology varies widely. The refinement of surgical techniques and the advent of more effective chemotherapy in the past 25 years has increased overall survival rates from approximately 20% to 70%, thus improving the outcome for girls with malignant tumors. This article summarizes the current evaluation and management of ovarian masses in childhood and reviews pertinent pathology. AORN J 67 (March 1998) 568-576.

BODY:
The article "Ovarian masses in the pediatric patient" is the basis for this AORN Journal independent study. The behavioral objectives and examination for this program were prepared by Helen Starbuck Pashley, RN, MA, CNOR, with consultation from Trish O'Neill, RN, MS, professional education specialist, Center for Perioperative Education.

A minimum score of 70% on the multiple-choice examination is necessary to earn one contact hour for this independent study. Participants receive feedback on incorrect answers. Each applicant who successfully completes this study will receive a certificate of completion. The deadline for submitting this study is March 31, 1999.

Send the completed application form, multiple-choice examination, learner evaluation, and appropriate fee to

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BEHAVIORAL OBJECTIVES

After reading and studying the article on ovarian masses in the pediatric patient, the nurse will be able to

(1) discuss the incidence of ovarian tumors in the pediatric population,

(2) describe the types of ovarian tumors common to the pediatric patient,

(3) identify the signs and symptoms of pediatric ovarian tumors, and

(4) discuss the treatment of pediatric ovarian masses.

Pediatric ovarian masses are rare. The estimated incidence of all childhood ovarian lesions is 2.6 cases per 100,000 girls per year.(1) In children less than 15 years of age, malignant ovarian tumors comprise roughly 1% of all cancers.(2) Although experience at pediatric institutions varies, on average, 16% to 55% of pediatric ovarian lesions are malignant.(3) Estimating the risk of malignancy by age may also vary between institutions. Some authors report a higher risk for girls less than nine years of age.(4) Statistics from the Children's Hospital of Philadelphia show that children over nine years of age appear to be at greater risk.(5)

Non-neoplastic or purely cystic lesions represent one third of pediatric ovarian masses and are benign.(6) The predominant nonneoplastic lesion is a functional or follicular cyst that most frequently occurs in the postmenarchal adolescent, although cysts may be present in the neonate secondary to maternal human chorionic gonadotropin ([Beta]HCG) stimulation of the fetal ovaries. While childhood ovarian masses may present in utero through adolescence, most affected children are diagnosed between 10 and 14 years of age.

Pediatric ovarian masses display a broad range of pathology with varying clinical behavior. Despite the overall rarity of ovarian masses in the pediatric population, the relatively high potential for malignancy necessitates prompt evaluation and treatment. Current goals of therapy should be aimed at cure and preservation of fertility.

PRESENTATION

Pediatric ovarian masses occur as a variety of pathologic subtypes, each presenting with a relatively similar pattern of symptoms and signs. The most frequently encountered complaint of girls harboring an ovarian mass is abdominal pain.(7) The pain is typically mid-abdominal, because the ovaries, attached to an elongated pedicle, do not descend into the pelvis until puberty. As a result, ovarian masses may mimic other intraabdominal, processes, specifically appendicitis or other tumors.

Pain associated with these masses may be either acute, subacute, or chronic. When torsion of the ovary on its vascular pedicle with infarction occurs, severe and unremitting pain results. Physical findings are often consistent with what is known as an "acute abdomen" (ie, pain, tenderness, guarding, nausea, vomiting) and may be easily confused with acute appendicitis. Interestingly, the majority of pediatric ovarian masses may present on the right side, although without good explanation.(8) Other children may have a more insidious pattern of less severe abdominal discomfort that fluctuates and persists over weeks to months and is often ascribed to such processes as gastroenteritis or irritable bowel. Common constitutional symptoms may include nausea, emesis, fever, and anorexia. Parents may find an abdominal mass, fullness, or distension when bathing a young girl or during play. Prepubertal girls may present with precocious puberty if their tumors are hormonally active, and display premature secondary sex characteristics (eg, enlargement of breast buds, areolar discoloration, pubic hair, vaginal bleeding, vulvar hypertrophy).(9) Other less common symptoms include urinary frequency, dysuria, and intestinal obstruction when these structures are involved.

DIAGNOSTICS EVALUATION

As with any medical dilemma, an accurate diagnosis begins with a thorough history and physical examination, addressing those signs and symptoms noted above. A complete review of systems also is important to elicit the possibility of disseminated disease. On examination, a suprapubic mass, often extending above the umbilicus, is frequently palpable (Figure 1). Torsion of the tumor and ovary may lead to necrosis with localized peritoneal irritation and tenderness on abdominal palpation (Figure 2).

[Figure 1-2 ILLUSTRATION OMITTED]

The ovary is not the most common origin of symptomatic abdominal masses in the female pediatric patient, therefore, further data are helpful in establishing the correct diagnosis. Initial diagnostic tools should include abdominal radiographs to evaluate the bowel gas pattern and to exclude other abdominal processes. These films may reveal findings suggestive of ovarian pathology, including intraabdominal calcifications and teeth consistent with a teratoma or displacement of bowel gas representing a nonspecific mass effect.(10) Transabdominal ultrasonography of the ovaries is the best tool for establishing the origin and volume of a given mass and to distinguish cystic from solid tumors. Predominantly solid tumors with a thickened capsule and irregular contour are highly suspicious for malignancy. (11) Although computerized tomography scans and magnetic resonance imaging have been proposed as initial diagnostic tools, these technologies rarely add information not ascertained with sonographic techniques and are usually reserved for staging purposes.

A battery of studies including liver function tests and a complete blood count are helpful in assessing the patient's overall metabolic state and the integrity of her bone marrow function. Tumor markers, specifically [Beta]HCG, alpha fetoprotein ([Alpha]FP), cancer antigen (CA-125), and carcinoembryonic antigen (CEA), should be obtained before beginning definitive care to follow the patient's response to therapy and to monitor for recurrence of disease. Metastatic evaluation should include routine chest radiographs and should be carried out according to specific symptoms.

EMBRYOLOGY

In order to understand the broad range of ovarian pathology and the clinical significance of each tumor, one must review the embryological origins of the various histologic subtypes. (12) The developed ovary consists of three functioning cell types, the oocyte or egg, the follicular cells, and the supporting stromal cells. Each of these cell types can develop into a distinct class of ovarian tumor.

Oocytes are derivatives of the primordial germ cells that can result in germ cell tumors and represent the most common benign or malignant pediatric ovarian masses. Follicular cells are of epithelial origin and are important in regulating estrogen production and maturation of the follicle. These cells give rise to epithelial tumors, which are common adult masses but infrequent childhood lesions. The stromal granulosa and theca cells are of mesenchymal origin. They surround the follicular cells, support their development, and are the origin of stromal mesenchymal tumors, the least frequent variety of both pediatric and adult ovarian lesions. Any of these cell lineages may acquire neoplastic properties, resulting in the development of a wide array of histologic subtypes with variable clinical implications.

PATHOLOGY

Ovarian masses in childhood have numerous histologic subtypes as a result of their three cell type origins.(13) Although the pediatric spectrum of pathology is similar to that encountered in the adult population, the relative frequency and clinical behavior of each tumor differ between children and adults. Germ cell tumors comprise over two thirds of pediatric ovarian

masses, epithelial tumors 17%, stromal tumors 13%, and the remaining 3% are an "other" category that includes such processes as lymphomas.(14) Clinical outcome is strongly influenced by tumor subtype, therefore, an accurate histologic diagnosis is imperative. It is common for a young girl with an ovarian lesion to harbor a benign, mature, cystic teratoma of germ cell derivation.(15) A malignant ovarian mass in a young girl is most likely to be a germ cell tumor, commonly a dysgerminoma.(16) In contrast, adult patients often have follicular cysts if benign and epithelial carcinomas if malignant masses are present.

Germ cell tumors. The most common benign and malignant ovarian tumors affecting the pediatric population are of germ cell derivation. A variety of tumor subtypes exist. Benign germ cell tumors are largely represented by mature cystic teratomas, also referred to as dermoids. Malignant germ cell masses include dysgerminomas, immature teratomas, endodermal sinus tumors, embryonal carcinomas, choriocarcinomas, and mixed germ cell tumors. Mixed germ cell tumors are composed of two or more germ cell subtypes.

Purely cystic teratomas typically are 80% benign and rarely (1% to 3%) malignant.(17) These tumors are composed of elements derived from each of the three primordial germ layers, the ectoderm, mesoderm, and endoderm. Mature cystic teratomas often contain skin appendages, neural tissue, cartilage, bone, respiratory epithelium, pancreas, and intestinal epithelia (Figure 3). As a result, ovarian teratomas commonly demonstrate intraabdominal calcifications on x-ray and may be associated with elevated serum levels of [Alpha]FP. Cystic teratomas tend to be bilateral in approximately 12% of pediatric patients's and frequently have a diameter greater than 10 cm. Simple cystectomy with preservation of the remaining ovarian tissue, or oophorectomy in cases of complete replacement of the ovary, suffice as treatment.(19) One should inspect the contralateral ovary because of the incidence of bilateral disease.

[Figure 3 ILLUSTRATION OMITTED]

Roughly 20% of all teratomas are solid, of which 50% are estimated to be malignant.(20) Malignancy is determined by the degree of immature elements within the tumor. Immature teratomas may contain elements of the various primordial germ layers, although the more aggressive tumors typically contain a predominance of immature neuroepithelium. Solid teratomas may present with peritoneal seeding of their neuroglial elements, which are referred to as gliomatosis peritonei. These peritoneal implants, when possessing mature histology, usually regress following resection of the primary tumor.

Immature teratomas spread via the peritoneal fluid and do not demonstrate distant lymphatic or hematogenous metastasis. The deleterious effects of these tumors result from mechanical and metabolic derangements secondary to the malignant ascites. Given the significant risk for malignancy, girls with solid teratomas should have aggressive surgery including unilateral salpingo-oophorectomy, omentectomy, periaortic lymphadenectomy, close inspection of all peritoneal surfaces with biopsy as indicated, and intraoperative ultrasonography of the contralateral ovary. Radical exenteration (ie, total abdominal hysterectomy with bilateral salpingo-oophorectomy) should be avoided. Postoperative chemotherapy should be considered if the pathology reveals malignant elements. A second surgical examination of the area should follow within four months to assess efficacy of therapy. Overall survival is 70% for malignant teratomas.(21)

Dysgerminomas are the most common of the malignant germ cell tumors. These tumors present at an average age of 16 years, can be quite large, with tumor diameters often exceeding 20 cm, and are bilateral in 10% of affected girls.(22) Operative management is similar to that: described for immature teratomas, although total abdominal hysterectomy and bilateral salpingo-oophorectomy may rarely be indicated with more extensive disease. As these tumors are radiosensitive, postoperative radiotherapy may be wan-anted. Overall survival rates approach 80%.(23)

Other less common malignant germ cell tumors include endodermal sinus tumors, embryonal carcinomas, choriocarcinomas, and mixed germ cell tumors. These lesions tend to behave aggressively, necessitating more radical resection. On the whole they respond poorly to adjuvant chemotherapy and thus remain highly lethal.

Epithelial tumors. While tumors of epithelial origin are the most frequent type encountered in the adult population, these are rare in the pediatric patient and are limited to postmenarchal girls. In childhood, more than 50% of these tumors are malignant.(24)

Benign epithelial tumors include papillary and nonpapillary serous cystadenomas and mucinous cystadenomas. These lesions tend to be smooth and well circumscribed. Cystadenomas, are amenable to partial oophorectomy. Bilateral tumors are common.

Malignant epithelial tumors follow similar pathologic nomenclature, with either serous or mucinous cystadenocarcinomas. The serous cystadenocarcinoma occurs with greater frequency and is generally more aggressive. Bilateral disease is present in approximately 50% of patients affected with the serous tumors and less commonly with mucinous tumors. (25)

Stromal tumors, Stromal or mesenchymal tumors are the least frequently encountered of pediatric ovarian masses. Nearly 50% of stromal tumors will be hormonally active resulting in signs of precocious puberty secondary to estrogen production.(26) In childhood, the most common type of this tumor is the granulosa cell tumor. The majority of granulosa cell tumors are benign although often they are hormonally active. The incidence of malignancy is reported at less than one third of cases.(27) Theca cell tumors are rarer though they also may present with precocity. These lesions are invariably benign.

Arrhenoblastomas, or Sertoli-Leydig cell tumors, are rare as well in the pediatric population. Because of overproduction of androgen precursors, these tumors present with virilizing symptoms, typically amenorrhea, masculine body habitus, deepening of voice, clitoral enlargement, hirsutism, and reduction in breast size. Familial associations have been recognized.

Functional cysts. These lesions are benign, unilocular cysts that typically arise in adolescence, although they may occur with a relatively high frequency in female neonates. Cyst development in utero is driven by maternal [Beta]HCG while cysts in older children respond to follicle stimulating hormone. Generally these lesions will resolve spontaneously, although they may torse when enlarged or produce sexual precocity when lined with functional granulosa cells. In both situations resection of the cyst is needed.

Large simple cysts, which are otherwise uncomplicated, may be managed by aspiration, marsupialization, or cystectomy while attempting to salvage functional ovarian tissue. Additionally, premenarchal girls with large cysts should be evaluated for other possible sources of excess hormonal-axis stimulation. A palpable ovarian cyst in a neonate has a risk of torsion with ischemic loss of the ovary, thus prompting consideration of surgical decompression or cystectomy.(28) Most neonatal cysts will regress spontaneously, however, and asymptomatic babies should be carefully observed for two months to track resolution of the cyst.

MANAGEMENT

Despite the wide array of pediatric ovarian masses, surgical techniques have evolved that optimize care and avoid dilemmas. The goals of therapy are to cure the patient and to preserve fertility. A successful outcome is dependent on a multidisciplinary approach, including the perioperative nursing team, the surgeons, anesthesia care personnel, and the oncologists.

PERIOPERATIVE NURSING CARE

Preoperative care of the child with an ovarian mass involves extensive teaching of the patient and family by the perioperative nurse. This education includes a description of diagnostic procedures and why they are indicated, as well as a discussion of the preoperative diagnosis. The patient's age will dictate what materials will be best suited to enhance her understanding and experience. At the Children's Hospital of Philadelphia, the perioperative staff members use dolls, drawings, books, anatomic diagrams, and specific procedure-oriented teaching aids to educate the child and her family members about the surgical experience. An explanation of the surgical procedure and a tour of the operating suite and recovery room is an excellent way to make the child and the family more comfortable in the hospital environment. The patient's and family's specific concerns regarding body image, fertility, malignancy, or other age-appropriate matters should also be addressed perioperatively by the patient care team.

INTRAOPERATIVE NURSING CARE

After reviewing the patient's medical record, laboratory values, and surgical/anesthetic consents, the perioperative nurse meets with the patient and family to assess the patient and to answer any further questions. Because these tumors can occur in children from birth to adolescence, the nurse must assess the patient's developmental and intellectual status and tailor his or her approach to each child's circumstance. For example, while all children will be apprehensive, this apprehension may manifest itself differently in an infant or toddler than it would in a school age child or adolescent. Establishing a trusting relationship between the child and the perioperative nurse helps ease this apprehension for both the child and the family. The perioperative nurse should present clear, easy to understand, age-appropriate explanations regarding the surgical experience to the child while in the family's presence, knowing that fear of the unknown and the overall stress of a surgical experience may interfere with the child's and the parent's abilities to understand.(29)

Common developmental fears that children experience are fear of bodily injury, separation from or loss of parents, fears of the unknown, loss of self-control. Or loss of modesty. Through the use of simple explanations, willingness to answer questions, allowing the parents to accompany the child whenever possible, letting the child wear personal items of clothing or bring transitional security objects to the operating room, and the use of distractions such as storytelling, breathing, or counting, the nurse can help the child to cope successfully with this experience.(30)

When the perioperative nurse has finished his or her preoperative assessment of the patient record and the child and family, he or she escorts the patient to the operating suite. The surgical team positions the patient supine on the OR bed and the perioperative nurse places a safety belt across the patient's thighs, and pads all pressure points. After induction of general anesthesia, the anesthesia care provider places an IV and administers a broad-spectrum antibiotic and intubates the patient endotracheally. The perioperative nurse places a grounding pad on the patient's thigh, and inserts a size-appropriate Foley catheter. The anesthesia care provider also may place a nasogastric tube, and, depending on the surgeon's preference and the patient's age, may place an epidural catheter for intraoperative and postoperative analgesia. The perioperative nurse is also responsible for the disposition of all specimens to the appropriate laboratories.

SURGICAL AND MEDICAL CARE

When the surgeon suspects a benign mass based on preoperative evaluation, simple cystectomy or partial oophorectomy usually will suffice. These procedures may be performed using the traditional open abdominal approach or newer laparoscopic techniques. If, however, the surgeon suspects a malignant mass, the approach must be tailored to each ovarian tumor.(31) An adequate abdominal exploration often requires open abdominal surgery with a generous lower abdominal transverse or midline incision.

Initially, the surgeon determines the extent of the tumor's presence by meticulous inspection of all peritoneal surfaces, including the diaphragm. The surgeon samples peritoneal implants for malignant histology, and resects the involved ovary. Depending on the malignant cell type, he or she may resect the ipsilateral fallopian tube and broad ligament with the ovary (unilateral salpingo-oophorectomy). Fallopian tube remnants should be avoided in order to prevent future cornual or ectopic pregnancy. The surgeon must inspect the contralateral ovary carefully for occult tumor due to the frequency of bilateral disease that may be accomplished with intraoperative ultrasound or the ovary may be bivalved as indicated. If the tumor is malignant or clinical suspicion of malignancy is high, the surgeon performs an omentectomy and periaortic lymph node dissection.

Important goals of pediatric surgical oncology include preservation of hormonal function and future fertility. Therefore, the initial procedure is often limited to oophorectomy, and further surgical strategy is dictated by the final pathology report. Only if the contralateral ovary and uterus involvement is extensive, or if they contain aggressive tumors, are exenterating procedures indicated. Incidental appendectomy should be performed to exclude appendicitis as an etiology of any future abdominal or pelvic complaints in these girls.

For malignant tumors, postoperative combination chemotherapy has proven beneficial, and overall survival rates have increased from 20% to 70% since the early 1970s.(32) Alternating cycles of vinblastine, bleomycin, and cisplatin, and actinomycin D. cyclophosphamide, and adriamycin are frequently administered, as originally developed by the Children's Cancer Group. A second laparotomy is often performed four to six months following completion of the initial round of chemotherapy to assess therapeutic efficacy. Radiation therapy is of limited use in pediatric ovarian malignancies because generally these tumors respond poorly. Radiation therapy is restricted to use with dysgerminomas.

POSTOPERATIVE CARE

The anesthesia care provider generally extubates the patient immediately following surgery and with the perioperative nurse and surgeon, transports the patient to the postanesthesia care unit. The patient's postoperative course is largely dependent on the final diagnosis, and final pathology results are usually available within 48 hours. If the mass is malignant, decisions regarding follow-up care will include chemotherapy, radiation therapy, and further surgery. If the mass is benign, the child generally is discharged in several days and has a follow-up visit within a few weeks after surgery.

Physical assessment (eg, for pain, infection, return to activities of daily living), pain management (ie, patient controlled analgesia for children older than seven years, IV, IM or oral analgesics for younger patients), and discharge planning for the child with a malignant mass are important postoperative nursing goals. The nurse will help the parents make arrangements for follow-up care, outpatient chemotherapy, emotional and educational support, and arrange for any other necessary home care services. The patient and family will require considerable emotional support and education during this time and coordination with social services and home health providers is often needed.

CONCLUSION

Pediatric ovarian masses Present a wide range of challenges to the patient and her family, as well as to the nursing staff members, surgeons, and oncologists. Although these childhood tumors are similar to their adult counterparts, the relative frequency of each type of tumor and their clinical behavior differ. The diagnosis of an ovarian mass should be considered in any young girl presenting with abdominal pain, fullness or distension, anorexia, constitutional symptoms, or pubertal precocity. While these symptoms are nonspecific and more commonly due to other causes, evaluation of the ovaries should be included in the patient's overall assessment. Fortunately, the majority of pediatric tumors are benign and can be managed in

a way that preserves ovarian function.

In children with malignancies, refinement of surgical techniques and advances in chemotherapeutic protocols have resulted in significant improvement of survival rates as well as preservation of fertility. Although the prognosis of pediatric ovarian tumors has improved significantly during the last quarter century, further research to determine the molecular biology and genetic behavior of these interesting tumors is important if significant future progress is to be made. No routine screening test currently exists for these tumors, and further improvements in outcome depend upon a high level of clinical suspicion directed toward any abdominal mass to provide early detection and treatment.

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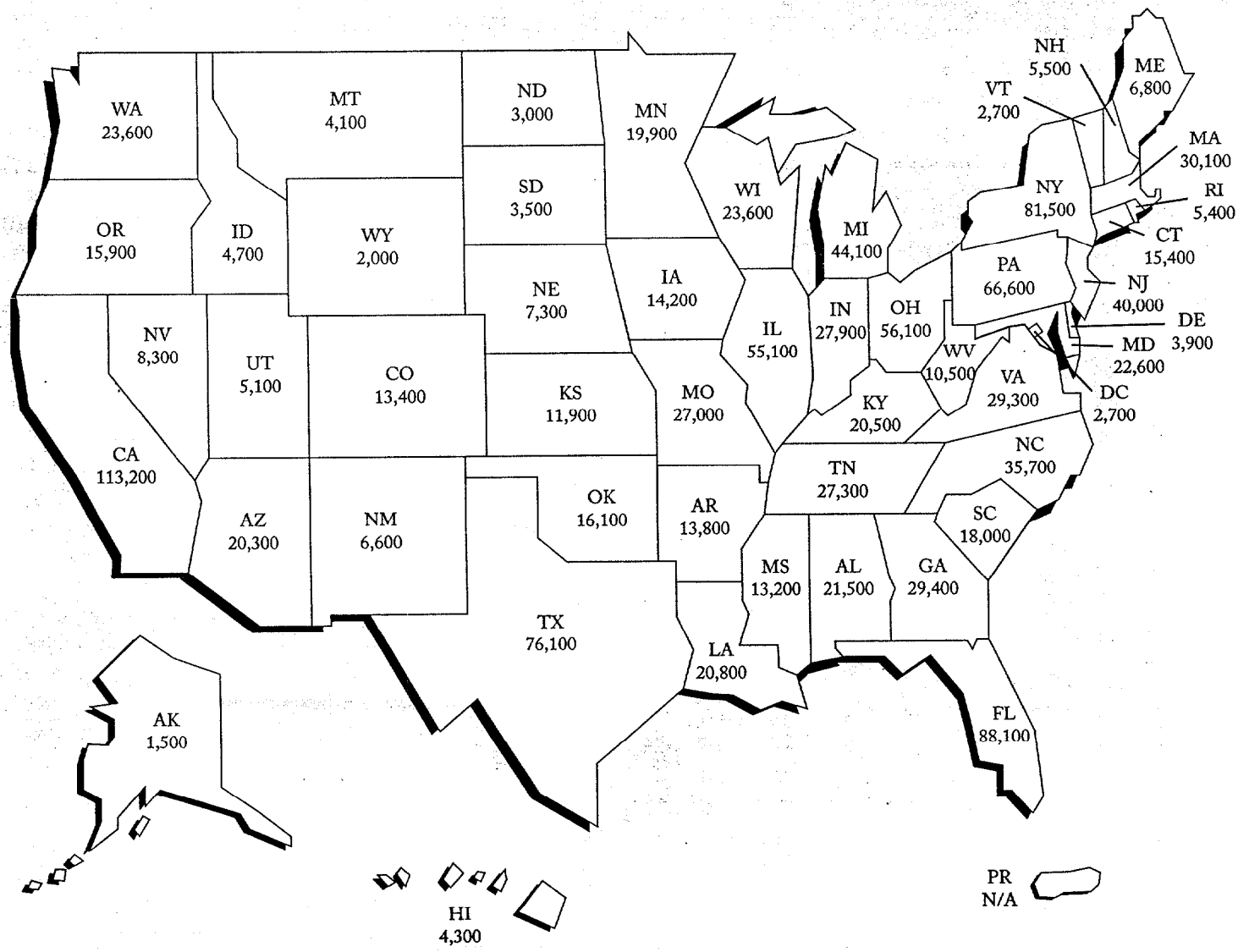

Estimated number of new cancer cases by state for 2000.
Estimated total number for the US: 1,220,100, excluding basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

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CANCER: BASIC FACTS

What Is Cancer?

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread is not controlled, it can result in death. Cancer is caused by both external (chemicals, radiation, and viruses) and internal (hormones, immune conditions, and inherited mutations) factors. Causal factors may act together or in sequence to initiate or promote carcinogenesis. Ten or more years often pass between exposures or mutations and detectable cancer. Cancer is treated by surgery, radiation, chemotherapy, hormones, and immunotherapy.

Can Cancer Be Prevented?

All cancers caused by cigarette smoking and heavy use of alcohol could be prevented completely. The ACS estimates that in 2000 about 171,000 cancer deaths are expected to be caused by tobacco use, and about 19,000 cancer deaths may be related to excessive alcohol use, frequently in combination with tobacco use.

Scientific evidence suggests that about one-third of the 552,200 cancer deaths expected to occur in 2000 are expected to be related to nutrition and other lifestyle factors and could also be prevented. Certain cancers are related to viral infections—for example, hepatitis B virus (HBV), human papillomavirus (HPV), human immunodeficiency virus (HIV), human T-cell leukemia/lymphoma virus-I (HTLV-I), and others—and could be prevented through behavioral changes. In addition, many of the 1.3 million skin cancers that are expected to be diagnosed in 2000 could have been prevented by protection from the sun's rays.

Regular screening examinations by a health care professional can result in the detection of cancers of the breast, colon, rectum, cervix, prostate, testis, oral cavity, and skin at earlier stages, when treatment is more likely to be successful. Self examinations for cancers of the breast and skin may also result in detection of tumors at earlier stages. The screening-accessible cancers listed above account for about half of all new cancer cases. The 5-year relative survival rate for these cancers is about 80%. If all Americans participated in regular cancer screenings, this rate could increase to 95%.

Who Is at Risk of Developing Cancer?

Anyone. Since the occurrence of cancer increases as individuals age, most cases affect adults middle-aged or older. Nearly 80% of all cancers are diagnosed at ages 55 and older. Cancer researchers use the word risk in different ways. *Lifetime risk* refers to the probability that an individual, over the course of a lifetime, will develop cancer or die from it. In the US, men have a 1 in 2 lifetime risk of developing cancer, and for women the risk is 1 in 3.

Relative risk is a measure of the strength of the relationship between risk factors and the particular cancer. It compares the risk of developing cancer in persons with a certain exposure or trait to the risk in persons who do not have this exposure or trait. For example, smokers have a 10-fold relative risk of developing lung cancer compared with nonsmokers. This means that smokers are about 10 times more likely to develop lung cancer (or have a 900% increased risk) than nonsmokers. Most relative risks are not this large. For example, women who have a first-degree (mother, sister, or daughter) family history of breast cancer have about a 2-fold increased risk of developing breast cancer compared with women who do not have a family history. This means that women with a first-degree family history are about two times or 100% more likely to develop breast cancer than women who do not have a family history of the disease.

All cancers involve the malfunction of genes that control cell growth and division. About 5% to 10% of cancers are clearly hereditary, in that an inherited faulty gene predisposes the person to a very high risk of particular cancers. The remainder of cancers are not hereditary, but result from damage to genes (mutations) that occurs throughout our lifetime, either due to internal factors, such as hormones or the digestion of nutrients within cells, or external factors, such as chemicals and sunlight.

How Many People Alive Today Have Ever Had Cancer?

The National Cancer Institute estimates that approximately 8.4 million Americans alive today have a history of cancer. Some of these individuals can be considered cured, while others still have evidence of cancer and may be undergoing treatment.

How Many New Cases Are Expected to Occur This Year?

About 1,220,100 new cancer cases are expected to be diagnosed in 2000. Since 1990, approximately 13 million new cancer cases have been diagnosed. These estimates do not include carcinoma in situ (noninvasive cancer) of any site except urinary bladder, and do not include basal and squamous cell skin cancers. Approximately 1.3 million cases of basal and squamous cell skin cancers are expected to be diagnosed this year.

How Many People Are Expected to Die of Cancer This Year?

This year about 552,200 Americans are expected to die of cancer—more than 1,500 people a day. Cancer is the second leading cause of death in the US, exceeded only by heart disease. In the US, 1 of every 4 deaths is from cancer.

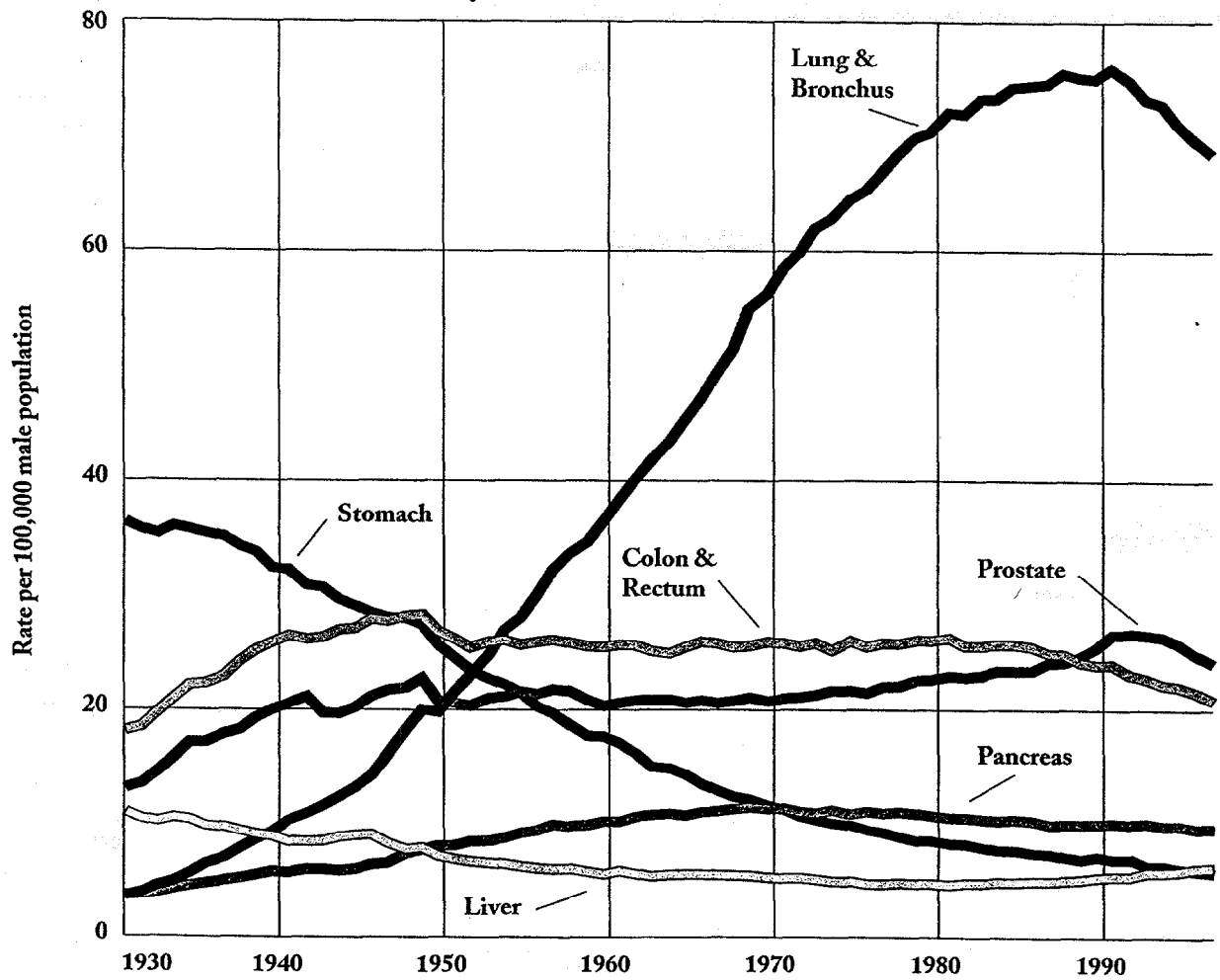
What Percentage of People Survive Cancer?

Five-year relative survival rates are commonly used to monitor progress in the early detection and treatment of cancer. The *relative survival rate* is the survival rate observed for a group of cancer patients compared to the survival rate for persons in the general population who are similar to the patient group with respect to age, gender, race, and calendar year of observation. Relative survival adjusts for normal life expectancy (factors such as dying of heart disease, accidents, and diseases of old age). *Five-year relative survival rates* include persons who are living five years after diagnosis, whether in remission, disease-free, or under treatment. While these rates provide some indication about the average survival experience of cancer patients in a given population, they are less informative when used to predict individual prognosis and should be interpreted with caution. First, 5-year relative survival rates are based on patients who were diagnosed and treated at least eight years ago and do not reflect recent advances in treatment. Second, information about detection methods, treatment protocols, additional illnesses, and behaviors that influence survival are not taken into account in the estimation of survival rates. The 5-year relative survival rate for all cancers combined is 59%.

How is Cancer Staged?

Staging is the process of describing the extent of the disease or the spread of cancer from the site of origin. Staging is essential in determining the choice of therapy and assessing prognosis. A cancer's stage is based on

Age-Adjusted Cancer Death Rates,* Males by Site, US, 1930–1996



*Per 100,000, age-adjusted to the 1970 US standard population. **Note:** Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung & bronchus, and colon & rectum are affected by these coding changes.

Source: US Mortality Public Use Data Tapes 1960–1996, US Mortality Volumes 1930–1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999.

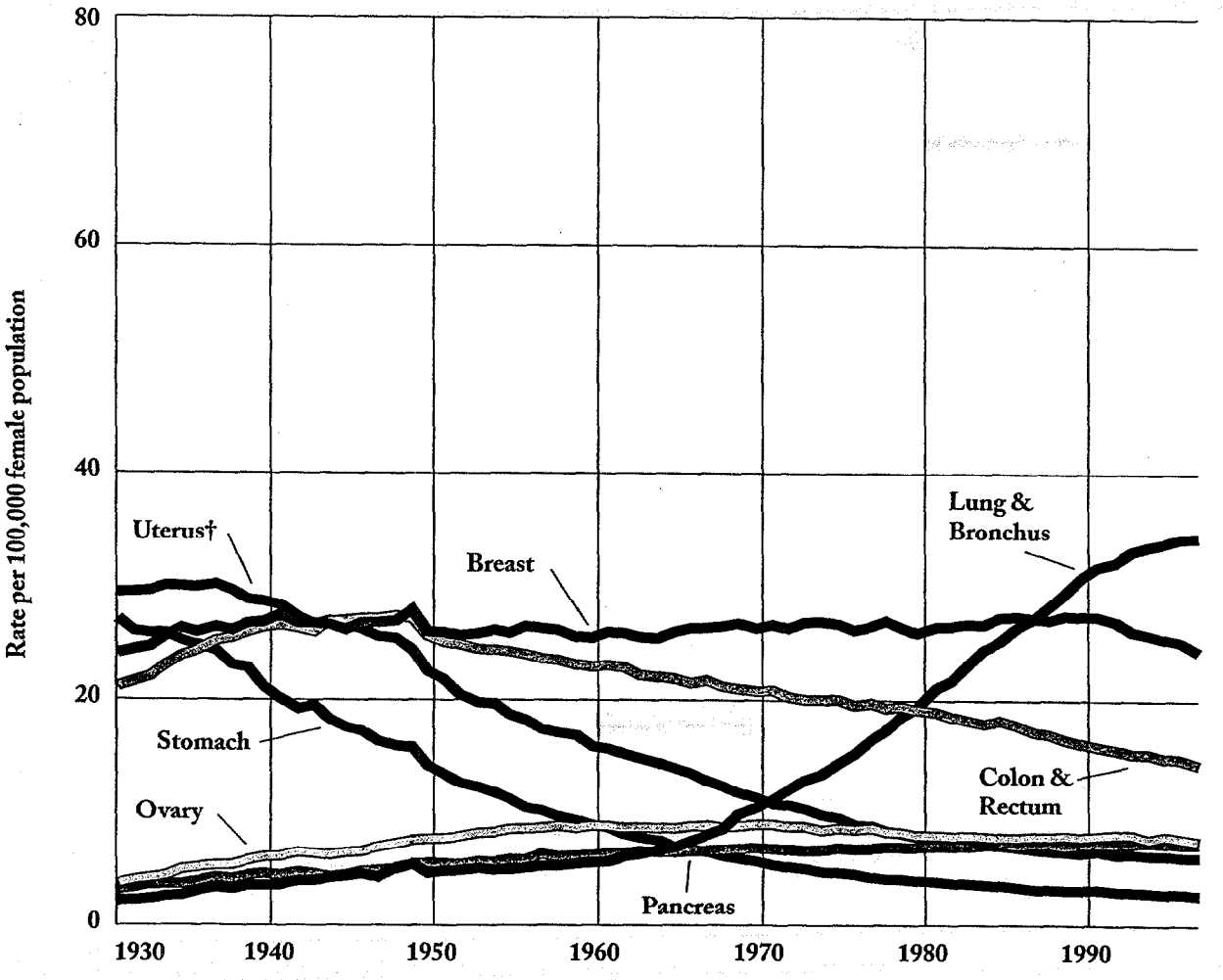
American Cancer Society, Surveillance Research

information about the primary tumor's size and location in the body and whether or not it has spread to other areas of the body. A number of different staging systems are currently being used to classify tumors. The TNM staging system assesses tumors in three ways: extent of the primary tumor (T), absence or presence of regional lymph node involvement (N), and absence or presence of distant metastases (M). Once the T, N, and M are determined, a "stage" of I, II, III, or IV is assigned, with stage I being early stage and IV being advanced stage. Summary staging (in situ, local, regional, and distant) has been useful for descriptive and statistical analysis of tumor registry data. If cancer cells are present only in the layer of cells they developed in and they have not spread to other parts of that organ or elsewhere in the body, then the stage is in situ. If cancer cells have spread beyond the original layer of tissue, then the cancer is considered invasive. Please see the table on page 14 for a description of the other summary stage categories.

What Are the Costs of Cancer?

The National Institutes of Health estimate overall annual costs for cancer at $107 billion; $37 billion for direct medical costs (total of all health expenditures), $11 billion for indirect morbidity costs (cost of lost productivity due to illness), and $59 billion for indirect mortality costs (cost of lost productivity due to premature death). Treatment of breast, lung, and prostate cancers account for over half of the direct medical costs. Insurance status and barriers to health care may affect the cost of treating cancer in this country. According to 1996 data, about 19% of Americans under age 65 have no health insurance, and about 26% of older persons have only Medicare coverage. During 1996, almost 18% of Americans reported not having a usual source of health care. Also, 12% of American families had members who experienced difficulty or delay in obtaining care or did not receive needed health care services.

Age-Adjusted Cancer Death Rates,* Females by Site, US, 1930–1996



*Per 100,000, age-adjusted to the 1970 US standard population. †Uterus cancer death rates are for uterine cervix and uterine corpus combined. **Note:** Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung & bronchus, and colon & rectum are affected by these coding changes.

Source: US Mortality Public Use Data Tapes 1960–1996, US Mortality Volumes 1930–1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 1999. American Cancer Society, Surveillance Research

Estimated New Cancer Cases and Deaths by Sex for All Sites, United States, 2000*

	Estimated New Cases			Estimated Deaths		
	Both Sexes	Male	Female	Both Sexes	Male	Female
All Sites	1,220,100	619,700	600,400	552,200	284,100	268,100
Oral cavity & pharynx	30,200	20,200	10,000	7,800	5,100	2,700
Tongue	6,900	4,500	2,400	1,700	1,100	600
Mouth	10,900	6,500	4,400	2,300	1,300	1,000
Pharynx	8,200	5,900	2,300	2,100	1,500	600
Other oral cavity	4,200	3,300	900	1,700	1,200	500
Digestive system	226,600	117,600	109,000	129,800	69,300	60,500
Esophagus	12,300	9,200	3,100	12,100	9,200	2,900
Stomach	21,500	13,400	8,100	13,000	7,600	5,400
Small intestine	4,700	2,300	2,400	1,200	600	600
Colon	93,800	43,400	50,400	47,700	23,100	24,600
Rectum	36,400	20,200	16,200	8,600	4,700	3,900
Anus, anal canal, & anorectum	3,400	1,400	2,000	500	200	300
Liver & intrahepatic bile duct	15,300	10,000	5,300	13,800	8,500	5,300
Gallbladder & other biliary	6,900	2,900	4,000	3,400	1,200	2,200
Pancreas	28,300	13,700	14,600	28,200	13,700	14,500
Other digestive organs	4,000	1,100	2,900	1,300	500	800
Respiratory system	179,400	101,500	77,900	161,900	93,100	68,800
Larynx	10,100	8,100	2,000	3,900	3,100	800
Lung & bronchus	164,100	89,500	74,600	156,900	89,300	67,600
Other respiratory organs	5,200	3,900	1,300	1,100	700	400
Bones & joints	2,500	1,500	1,000	1,400	800	600
Soft tissue (including heart)	8,100	4,300	3,800	4,600	2,200	2,400
Skin (excluding basal & squamous)	56,900	34,100	22,800	9,600	6,000	3,600
Melanoma-skin	47,700	27,300	20,400	7,700	4,800	2,900
Other non-epithelial skin	9,200	6,800	2,400	1,900	1,200	700
Breast	184,200	1,400	182,800	41,200	400	40,800
Genital system	265,900	188,400	77,500	59,000	32,500	26,500
Uterine cervix	12,800	—	12,800	4,600	—	4,600
Uterine corpus	36,100	—	36,100	6,500	—	6,500
Ovary	23,100	—	23,100	14,000	—	14,000
Vulva	3,400	—	3,400	800	—	800
Vagina & other genital, female	2,100	—	2,100	600	—	600
Prostate	180,400	180,400	—	31,900	31,900	—
Testis	6,900	6,900	—	300	300	—
Penis & other genital, male	1,100	1,100	—	300	300	—
Urinary system	86,700	58,600	28,100	24,600	15,700	8,900
Urinary bladder	53,200	38,300	14,900	12,200	8,100	4,100
Kidney & renal pelvis	31,200	18,800	12,400	11,900	7,300	4,600
Ureter & other urinary organs	2,300	1,500	800	500	300	200
Eye & orbit	2,200	1,200	1,000	200	100	100
Brain & other nervous system	16,500	9,500	7,000	13,000	7,100	5,900
Endocrine system	20,200	5,600	14,600	2,100	1,000	1,100
Thyroid	18,400	4,700	13,700	1,200	500	700
Other endocrine	1,800	900	900	900	500	400
Lymphoma	62,300	35,900	26,400	27,500	14,400	13,100
Hodgkin's disease	7,400	4,200	3,200	1,400	700	700
Non-Hodgkin's lymphoma	54,900	31,700	23,200	26,100	13,700	12,400
Multiple myeloma	13,600	7,300	6,300	11,200	5,800	5,400
Leukemia	30,800	16,900	13,900	21,700	12,100	9,600
Acute lymphocytic leukemia	3,200	1,800	1,400	1,300	700	600
Chronic lymphocytic leukemia	8,100	4,600	3,500	4,800	2,800	2,000
Acute myeloid leukemia	9,700	4,800	4,900	7,100	3,900	3,200
Chronic myeloid leukemia	4,400	2,600	1,800	2,300	1,300	1,000
Other leukemia	5,400	3,100	2,300	6,200	3,400	2,800
Other & unspecified primary sites	34,000	15,700	18,300	36,600	18,500	18,100

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder. Carcinoma in situ of the breast accounts for about 42,600 new cases annually, and melanoma in situ accounts for about 28,600 new cases annually. Estimates of new cases are based on incidence rates from the NCI SEER program 1979-1996.

Estimated New Cancer Cases, by State, 2000*

State	All Sites	Female Breast	Uterine Cervix	Colon & Rectum	Uterine Corpus	Lung & Bronchus	Melanoma	Non-Hodgkin's Lymphoma	Kidney	Prostate	Urinary Bladder
Alabama	21,500	2,700	200	1,800	500	3,000	900	900	400	3,500	800
Alaska	1,500	200	†	200	†	200	100	100	†	100	100
Arizona	20,300	2,800	200	2,000	600	2,800	1,000	900	500	3,300	900
Arkansas	13,700	1,900	100	1,300	400	2,200	400	500	400	2,200	500
California	113,200	17,900	1,300	11,400	3,200	14,000	5,000	5,300	2,900	16,400	5,200
Colorado	13,400	2,000	100	1,400	400	1,500	700	700	400	1,800	600
Connecticut	15,400	2,300	100	1,500	500	1,900	600	700	400	2,300	800
Delaware	3,900	500	100	400	100	600	100	200	100	600	200
Dist. of Columbia	2,700	500	†	300	100	300	†	100	†	600	100
Florida	88,100	12,000	900	9,100	2,500	12,600	3,500	4,000	2,000	13,700	4,300
Georgia	29,400	4,600	400	2,800	900	4,200	1,000	1,000	700	4,400	1,000
Hawaii	4,300	500	†	400	100	500	100	200	100	700	100
Idaho	4,700	700	†	500	100	600	200	200	200	800	200
Illinois	55,100	8,900	600	6,000	1,600	7,300	1,900	2,500	1,400	7,800	2,400
Indiana	27,900	4,200	300	3,100	800	4,000	1,000	1,200	800	3,900	1,200
Iowa	14,200	2,100	100	1,900	600	1,900	500	700	400	2,200	600
Kansas	11,900	1,600	100	1,200	300	1,600	500	500	300	1,800	500
Kentucky	20,500	2,700	300	2,200	500	3,400	900	800	600	2,600	600
Louisiana	20,800	3,200	300	2,200	500	2,900	700	800	600	3,200	700
Maine	6,800	900	100	700	100	1,000	200	300	200	900	400
Maryland	22,600	3,700	300	2,600	700	3,100	800	900	500	3,300	1,000
Massachusetts	30,100	4,400	200	3,500	800	3,900	1,300	1,400	700	4,200	1,700
Michigan	44,100	6,700	400	4,800	1,400	6,100	1,400	2,100	1,200	6,600	2,100
Minnesota	19,900	2,800	200	2,000	500	2,300	700	1,100	600	3,300	1,000
Mississippi	13,200	2,000	200	1,300	200	1,900	400	500	300	2,200	300
Missouri	27,000	3,700	300	2,900	800	4,000	1,100	1,100	700	3,600	1,100
Montana	4,100	600	†	400	100	500	100	200	100	700	200
Nebraska	7,300	1,100	100	1,000	200	900	200	300	200	1,000	300
Nevada	8,300	1,000	100	900	200	1,200	400	300	200	1,200	400
New Hampshire	5,500	700	†	600	100	700	200	300	100	700	300
New Jersey	40,000	6,400	400	4,600	1,500	4,800	1,700	1,900	1,000	5,600	2,100
New Mexico	6,600	1,000	100	700	200	700	300	300	200	1,200	200
New York	81,500	13,700	1,000	9,200	3,200	9,800	2,600	3,800	1,900	11,800	4,100
North Carolina	35,700	5,200	400	3,700	1,100	5,200	1,300	1,400	900	5,300	1,400
North Dakota	3,000	500	†	400	100	300	100	100	100	500	100
Ohio	56,100	8,600	600	6,200	2,000	7,800	1,900	2,700	1,500	7,800	2,500
Oklahoma	16,100	2,400	200	1,700	300	2,500	700	700	500	2,100	700
Oregon	15,800	2,200	100	1,600	400	2,200	700	700	400	2,700	700
Pennsylvania	66,600	10,500	600	7,800	2,200	8,600	2,400	3,000	1,700	10,000	3,100
Rhode Island	5,400	800	100	600	100	800	200	300	100	700	300
South Carolina	18,000	2,600	200	1,900	500	2,500	500	700	500	2,900	800
South Dakota	3,500	400	†	400	100	400	200	200	100	600	100
Tennessee	27,300	3,800	400	2,900	600	4,200	1,300	1,200	700	3,600	900
Texas	76,100	11,500	1,000	8,300	2,100	10,700	3,400	3,600	2,200	11,300	2,800
Utah	5,100	900	100	600	200	400	400	300	100	1,200	200
Vermont	2,700	400	100	400	100	400	200	100	100	300	100
Virginia	29,300	4,500	300	2,900	1,000	4,000	1,200	1,200	700	4,400	1,100
Washington	23,600	3,500	200	2,300	600	3,100	1,100	1,100	600	3,200	1,000
West Virginia	10,500	1,400	100	1,100	300	1,600	400	400	300	1,300	400
Wisconsin	23,600	3,300	200	2,500	700	2,800	1,000	1,200	700	3,800	1,200
Wyoming	2,000	300	†	300	100	200	100	100	100	400	†
United States	1,220,100	182,800	12,800	130,200	36,100	164,100	47,700	54,900	31,200	180,400	53,200

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder. †Estimate is 50 or fewer cases. State case estimates between 51 and 99 were rounded to 100. **Note:** These estimates are offered as a rough guide and should be interpreted with caution. They are calculated according to the distribution of estimated cancer deaths in 2000 by state. State estimates may not add to US total due to rounding.

Estimated Cancer Mortality, by State, 2000*

State	All Sites	Female Breast	Colon & Rectum	Liver	Leukemia	Lung & Bronchus	Non-Hodgkin's Lymphoma	Ovary	Pancreas	Prostate	Stomach
Alabama	9,700	600	800	300	300	2,800	400	200	500	600	200
Alaska	700	100	100	†	†	200	†	†	†	†	†
Arizona	9,200	600	900	200	300	2,600	400	200	500	600	200
Arkansas	6,200	400	600	200	200	2,100	300	200	300	400	100
California	51,200	4,000	4,900	1,700	2,100	13,400	2,500	1,400	2,700	2,900	1,500
Colorado	6,100	400	600	100	300	1,400	300	100	300	300	100
Connecticut	7,000	500	600	200	300	1,900	300	200	400	400	200
Delaware	1,800	100	200	†	100	500	100	†	100	100	†
Dist. of Columbia	1,200	100	100	†	†	300	†	†	100	100	100
Florida	39,900	2,700	3,900	1,000	1,500	12,000	1,900	900	2,100	2,400	900
Georgia	13,300	1,000	1,200	300	500	4,000	500	400	600	800	300
Hawaii	2,000	100	200	100	100	500	100	†	100	100	100
Idaho	2,100	200	200	†	100	500	100	100	100	100	†
Illinois	24,900	2,000	2,600	700	1,000	6,900	1,200	700	1,300	1,400	600
Indiana	12,600	900	1,300	300	500	3,900	600	300	600	700	200
Iowa	6,400	500	800	100	300	1,800	300	200	300	400	100
Kansas	5,400	400	500	100	200	1,600	200	100	300	300	100
Kentucky	9,300	600	900	200	300	3,200	400	200	400	500	200
Louisiana	9,400	700	1,000	300	400	2,700	400	200	500	600	300
Maine	3,100	200	300	†	100	900	200	100	200	200	100
Maryland	10,200	800	1,100	200	400	2,900	400	200	500	600	300
Massachusetts	13,600	1,000	1,500	300	500	3,700	700	300	700	700	300
Michigan	20,000	1,500	2,100	500	700	5,800	1,000	500	1,000	1,200	400
Minnesota	9,000	600	900	200	400	2,200	500	200	500	600	200
Mississippi	6,000	400	600	200	200	1,800	200	100	300	400	100
Missouri	12,200	800	1,300	300	500	3,800	500	300	500	600	300
Montana	1,900	100	200	100	100	500	100	100	100	100	†
Nebraska	3,300	300	400	100	200	900	200	100	100	200	100
Nevada	3,800	200	400	100	100	1,200	200	100	200	200	100
New Hampshire	2,500	200	300	100	100	700	100	100	100	100	†
New Jersey	18,100	1,400	2,000	500	800	4,600	900	500	1,000	1,000	500
New Mexico	3,000	200	300	100	100	700	100	100	100	200	100
New York	36,900	3,100	4,000	900	1,400	9,400	1,800	1,000	2,200	2,100	1,100
North Carolina	16,200	1,200	1,600	300	600	5,000	700	400	800	900	300
North Dakota	1,300	100	200	†	100	300	100	†	100	100	†
Ohio	25,400	1,900	2,700	500	1,000	7,400	1,300	600	1,300	1,400	500
Oklahoma	7,300	500	700	200	300	2,400	300	200	300	400	100
Oregon	7,100	500	700	100	300	2,100	300	200	400	500	100
Pennsylvania	30,100	2,300	3,400	700	1,200	8,200	1,400	800	1,500	1,800	600
Rhode Island	2,400	200	300	100	100	800	100	100	100	100	100
South Carolina	8,200	600	800	200	300	2,400	300	200	400	500	200
South Dakota	1,600	100	200	†	100	400	100	†	100	100	†
Tennessee	12,400	900	1,200	300	400	4,000	600	300	600	600	300
Texas	34,400	2,600	3,600	1,100	1,400	10,300	1,700	900	1,700	2,000	900
Utah	2,300	200	200	100	100	400	100	100	100	200	40
Vermont	1,200	100	200	†	†	400	100	†	†	100	†
Virginia	13,300	1,000	1,300	300	500	3,800	600	300	600	800	300
Washington	10,700	800	1,000	300	500	3,000	500	300	500	600	200
West Virginia	4,800	300	500	100	200	1,500	200	100	200	200	100
Wisconsin	10,700	700	1,100	200	500	2,700	600	300	600	700	200
Wyoming	900	100	100	†	†	200	†	†	†	100	†
United States	552,200	40,800	56,300	13,800	21,700	156,900	26,100	14,000	28,200	31,900	13,000

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder. †Estimate is 50 or fewer deaths. State death estimates between 51 and 99 were rounded to 100. **Note:** State estimates may not add to US total due to rounding.

Cancer Incidence (1991–1995) and Mortality (1992–1996) Rates,* by Site and State

	Breast		Colon & Rectum				Lung & Bronchus				Prostate	
	Female		Male		Female		Male		Female		Male	
State	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Alabama†	—	23.2	—	18.5	—	12.9	—	86.3	—	30.9	—	28.7
Alaska†	—	23.2	—	21.9	—	15.8	—	65.3	—	40.5	—	20.8
Arizona	95.6	22.3	42.9	18.4	29.2	12.4	64.6	61.1	36.3	31.8	118.8	23.2
Arkansas†	—	23.1	—	21.1	—	14.5	—	96.7	—	35.6	—	27.1
California‡	108.3	24.4	50.3	18.4	35.0	12.9	72.1	55.8	44.2	33.5	150.3	23.0
Colorado‡	106.5	21.6	46.5	17.7	33.5	12.4	62.3	49.6	33.6	25.5	166.3	23.9
Connecticut‡	117.3	25.7	59.8	21.6	41.3	13.9	78.6	59.3	46.7	33.1	148.4	23.1
Delaware‡	110.9	27.8	61.5	23.9	41.9	15.7	100.1	82.3	54.4	43.2	163.7	30.0
Dist. of Columbia†	—	32.8	—	25.2	—	17.7	—	79.3	—	34.6	—	45.4
Florida‡	103.2	24.5	56.8	19.9	40.0	13.6	83.2	70.2	46.8	35.9	138.1	23.1
Georgia†	—	24.0	—	19.2	—	13.5	—	86.7	—	31.6	—	31.7
Hawaii‡	99.3	17.6	55.9	17.4	36.3	11.6	62.4	45.9	30.8	22.3	119.5	16.8
Idaho‡	100.5	22.3	44.2	17.3	31.0	11.6	63.9	51.1	34.1	28.0	151.4	26.7
Illinois‡	107.2	27.5	56.7	24.2	39.9	16.0	85.3	73.4	42.7	34.6	133.5	25.8
Indiana	100.5	25.9	52.1	23.0	35.8	15.9	82.1	81.5	42.3	36.5	96.7	25.4
Iowa‡	107.3	24.6	59.2	22.0	43.4	15.6	83.9	66.9	38.5	30.0	147.0	24.2
Kansas†	—	23.4	—	20.6	—	13.1	—	65.7	—	31.0	—	24.1
Kentucky‡	95.9	24.8	53.7	24.0	38.9	16.3	117.9	102.3	51.9	42.7	113.7	25.2
Louisiana‡	96.4	26.4	53.9	22.8	38.8	15.7	110.6	92.8	44.8	36.2	147.7	30.8
Maine	102.4	25.3	58.6	23.5	42.3	17.1	92.0	78.5	45.9	39.8	122.9	26.4
Maryland	114.6	27.3	58.4	24.8	41.9	16.7	93.7	75.1	50.4	38.4	176.4	29.3
Massachusetts	119.2	27.9	61.6	24.8	40.6	16.3	78.8	66.5	45.4	36.6	147.5	24.8
Michigan‡	110.8	26.0	55.7	22.0	38.7	14.5	90.9	72.4	47.0	35.3	178.6	26.2
Minnesota‡	110.5	24.5	54.2	19.3	37.6	13.2	63.7	54.6	35.4	29.1	163.6	25.9
Mississippi†	—	23.8	—	20.5	—	13.4	—	91.1	—	31.1	—	32.6
Missouri†	—	24.6	—	22.4	—	14.9	—	82.0	—	36.4	—	24.5
Montana	107.7	24.6	47.4	19.8	34.3	12.9	67.6	57.8	40.2	32.0	148.7	26.9
Nebraska	100.9	24.8	52.9	23.3	36.1	14.4	70.5	63.1	32.8	27.6	151.6	21.5
Nevada	93.6	24.9	46.7	21.5	32.8	13.7	92.3	71.4	61.2	45.7	106.3	24.9
New Hampshire	110.6	27.5	56.0	22.6	42.3	17.2	78.5	69.1	46.9	39.2	142.0	24.6
New Jersey‡	115.0	28.4	65.7	25.7	44.7	16.9	82.9	66.2	44.7	34.2	161.6	26.3
New Mexico‡	95.0	23.1	40.8	17.6	28.5	11.5	53.7	46.5	29.8	24.5	148.9	24.8
New York	101.9	28.2	56.0	23.6	39.9	16.2	77.6	62.6	42.3	32.2	118.3	24.6
North Carolina	96.6	24.9	46.3	20.7	33.5	14.6	93.1	85.6	37.7	31.3	131.5	30.4
North Dakota†	—	24.4	—	22.0	—	14.0	—	56.3	—	24.7	—	28.8
Ohio†	—	27.2	—	23.9	—	15.9	—	78.5	—	36.7	—	26.1
Oklahoma†	—	24.2	—	19.3	—	13.9	—	83.5	—	35.1	—	23.5
Oregon†	—	24.0	—	18.4	—	13.0	—	64.3	—	40.0	—	24.8
Pennsylvania	108.7	27.7	62.1	24.6	42.6	16.7	84.0	71.0	40.0	32.5	146.1	25.8
Rhode Island‡	110.6	28.0	64.4	25.4	43.0	15.8	89.6	74.9	46.8	36.3	139.8	23.7
South Carolina†	—	24.4	—	22.0	—	14.6	—	83.4	—	30.3	—	32.8
South Dakota†	—	24.2	—	21.2	—	14.6	—	60.8	—	27.1	—	27.0
Tennessee	93.7	25.3	47.0	21.6	34.5	14.7	94.8	94.7	40.5	34.6	103.5	26.4
Texas	93.8	23.5	47.4	20.3	32.2	13.3	88.5	74.5	42.9	33.2	119.4	25.8
Utah‡	95.6	20.8	41.3	15.5	27.8	10.9	39.5	31.0	17.3	14.0	175.6	26.2
Vermont†	—	24.8	—	22.4	—	15.2	—	65.9	—	36.4	—	27.9
Virginia	92.9	25.8	45.2	21.2	32.8	15.1	78.1	78.6	36.4	34.3	128.6	29.1
Washington	116.5	24.1	46.8	18.5	35.8	13.2	74.4	63.3	50.0	37.0	132.6	23.9
West Virginia	95.0	23.4	51.7	22.4	40.1	15.6	102.1	87.2	51.2	41.5	112.1	24.4
Wisconsin‡	108.1	24.8	60.6	21.1	41.7	13.8	77.5	58.8	39.8	28.8	154.7	27.3
Wyoming‡	95.4	24.0	40.5	17.1	34.5	14.9	61.0	56.5	38.9	31.2	153.7	27.7
United States	110.6	25.4	53.0	21.5	37.6	14.6	75.9	70.8	42.8	33.8	156.5	25.6

*Per 100,000, age-adjusted to the 1970 US standard population. †This state's registry did not submit incidence data to the North American Association of Central Cancer Registries (NAACCR) for 1991–1995. ‡This state's registry has been recognized by NAACCR to meet the following data quality standards: data for all years 1991–1995; a NAACCR estimate of 0.1% duplicate records or fewer; resolution of errors detected using an EDITS software program; and a NAACCR estimate of at least 90% completeness.

Sources: Cancer in North America 1991–1995, North American Association of Central Cancer Registries: US Mortality 1973–1996, National Center for Health Statistics, Centers for Disease Control and Prevention 1999, SEER Incidence 1973–1996, Surveillance, Epidemiology and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

SELECTED CANCERS

BREAST

New Cases: An estimated 182,800 new invasive cases of breast cancer are expected to occur among women in the United States during 2000. About 1,400 new cases of breast cancer are expected to be diagnosed in men in 2000. After increasing about 4% per year in the 1980s, breast cancer incidence rates in women have leveled off in the 1990s to about 110.6 cases per 100,000.

Deaths: An estimated 41,200 deaths (40,800 women, 400 men) in 2000; breast cancer ranks second among cancer deaths in women. According to the most recent data, mortality rates declined significantly during 1992–1996 with the largest decreases in younger women—both white and black. These decreases are probably the result of earlier detection and improved treatment.

Signs and Symptoms: The earliest sign of breast cancer is usually an abnormality that shows up on a mammogram before it can be felt by the woman or her health care provider. When breast cancer has grown to the point where physical signs and symptoms exist, these may include a breast lump, thickening, swelling, distortion, or tenderness; skin irritation or dimpling; and nipple pain, scaliness, or retraction. Breast pain is very commonly due to benign conditions and is not usually the first symptom of breast cancer.

Risk Factors: The risk of breast cancer increases with age. The risk is higher in women who have a personal or family history of breast cancer, biopsy-confirmed atypical hyperplasia, a long menstrual history (menstrual periods that started early and ended late in life), or recent use of oral contraceptives or postmenopausal estrogens; who have never had children or had their first child after age 30, consume two or more drinks of alcohol daily, or have higher education and socioeconomic status. Worldwide, breast cancer incidence rates appear to correlate with variations in diet, especially fat intake, although a causal role for dietary factors has not been firmly established. Additional factors that may be related to breast cancer risk (increased or decreased) and that are currently being studied include pesticide and other chemical exposures, weight gain, induced abortion, physical inactivity, and selective estrogen-receptor modulators (SERMs) such as tamoxifen and raloxifene. Exciting new research about BRCA1 and BRCA2 susceptibility genes for breast cancer is also in progress, although, general screening of the population for these genes is not recommended.

Early Detection: Mammography is especially valuable as an early diagnostic tool because it can identify breast abnormalities that may be cancer at an early stage before physical symptoms develop. Numerous studies have shown that early detection increases survival and treatment options. The large declines in breast cancer mortality have been attributed, in part, to the use of regular screening mammography. The American Cancer Society recommends that women age 40 and older have an annual mammogram, an annual clinical breast examination by a health care professional, and perform monthly breast self-examination. Women ages 20–39 should have a clinical breast exam performed by a health care professional every three years and should perform monthly breast self-examination.

Most breast lumps are not cancer, but only a physician can make a diagnosis. When a woman has a suspicious lump or when a suspicious area is identified on a mammogram, diagnostic mammography can help determine whether additional tests are needed and if there are other lesions that are too small to be felt in the same or the opposite breast. All suspicious lumps should be biopsied for a definitive diagnosis.

Treatment: Taking into account the medical circumstances and the patient's preferences, treatment may involve lumpectomy (local removal of the tumor) and removal of the lymph nodes under the arm; mastectomy (surgical removal of the breast) and removal of the lymph nodes under the arm; radiation therapy; chemotherapy; or hormone therapy. Often, two or more methods are used in combination. Numerous studies have shown that, for early stage disease, long-term survival rates after lumpectomy plus radiotherapy are similar to survival rates after modified radical mastectomy. Patients should discuss possible options for the best management of their breast cancer with their physicians. Significant advances in reconstruction techniques provide several options for breast reconstruction after mastectomy. Recently, this has been done at the same time as the mastectomy.

Local excision of ductal carcinoma in situ (DCIS) with adequate amounts of surrounding normal breast tissue may prevent the local recurrence of the DCIS. Radiation to the breast and/or tamoxifen may reduce the chance of DCIS occurring in the remaining breast tissue. This is important because DCIS, if left untreated, may develop into invasive breast cancer.

Survival: The 5-year relative survival rate for localized breast cancer has increased from 72% in the 1940s to 96% today. If the cancer has spread regionally, however, the rate is 77%, and for women with distant metastases the rate is 21%. Survival after a diagnosis of breast

Leading Sites of New Cancer Cases and Deaths—2000 Estimates*

Cancer Cases by Site and Sex		Cancer Deaths by Site and Sex	
Male	**Female**	**Male**	**Female**
Prostate 180,400	Breast 182,800	Lung & bronchus 89,300	Lung & bronchus 67,600
Lung & bronchus 89,500	Lung & bronchus 74,600	Prostate 31,900	Breast 40,800
Colon & rectum 63,600	Colon & rectum 66,600	Colon & rectum 27,800	Colon & rectum 28,500
Urinary bladder 38,300	Uterine corpus 36,100	Pancreas 13,700	Pancreas 14,500
Non-Hodgkin's lymphoma 31,700	Non-Hodgkin's lymphoma 23,200	Non-Hodgkin's lymphoma 13,700	Ovary 14,000
Melanoma of the skin 27,300	Ovary 23,100	Leukemia 12,100	Non-Hodgkin's lymphoma 12,400
Oral cavity 20,200	Melanoma of the skin 20,400	Esophagus 9,200	Leukemia 9,600
Kidney 18,800	Urinary bladder 14,900	Liver 8,500	Uterine corpus 6,500
Leukemia 16,900	Pancreas 14,600	Urinary bladder 8,100	Brain 5,900
Pancreas 13,700	Thyroid 13,700	Stomach 7,600	Stomach 5,400
All Sites 619,700	All Sites 600,400	All Sites 284,100	All Sites 268,100

*Excludes basal and squamous cell skin cancer and in situ carcinomas except urinary bladder.

cancer continues to decline beyond five years. Seventy-one percent of women diagnosed with breast cancer survive 10 years, and 57% survive 15 years.

For more information about breast cancer, please inquire about the American Cancer Society publication *Breast Cancer Facts & Figures* (8610.99).

CHILDHOOD CANCER

New Cases: An estimated 8,600 new cases are expected to occur among children aged 0-14 in 2000; as a childhood disease, cancer is rare. Common sites include the blood and bone marrow, bone, lymph nodes, brain, sympathetic nervous system, kidneys, and soft tissues.

Deaths: An estimated 1,600 deaths are expected to occur among children aged 0-14 in 2000, about one-third of them from leukemia. Despite its rarity, cancer is the chief cause of death by disease in children under age 15. Mortality rates have declined 50% since 1973.

Early Detection: Cancers in children often are difficult to recognize. Parents should see that their children have regular medical checkups and should be alert to any unusual symptoms that persist. These include: an unusual mass or swelling; unexplained paleness and loss of energy; sudden tendency to bruise; a persistent, localized pain or limping; prolonged, unexplained fever or illness; frequent headaches, often with vomiting; sudden eye or vision changes; and excessive, rapid weight loss. Some of the main childhood cancers are:

- Leukemia which accounts for about 31.5% of cases in children ages 0-14 (see page 11).
- Osteosarcoma (2.4%), a bone cancer which may cause no pain at first; swelling in the area of the tumor is often the first sign.
- Ewing's sarcoma (1.7%), another type of cancer that arises in bone.
- Neuroblastoma (7.5%) which can appear anywhere but usually appears in the abdomen, where a swelling occurs.
- Rhabdomyosarcoma (3.4%), the most common soft tissue sarcoma, can occur in the head and neck area, genitourinary area, trunk, and extremities.
- Brain and intraspinal cancers (20.2%) which in early stages may cause headaches, frequently with nausea and vomiting; blurred or double vision, dizziness, and difficulty in walking or handling objects.

How to Estimate Cancer Statistics Locally, 2000

To obtain the estimated number of...	Multiply community population by: All Sites	Female Breast*	Colon & Rectum	Lung	Prostate*
New cancer cases	0.0044	0.0013	0.0005	0.0006	0.0013
Cancer deaths	0.0020	0.0003	0.0002	0.0006	0.0002
People who will eventually develop cancer	0.4064	0.1256	0.0559	0.0683	0.1591
People who will eventually die of cancer	0.2177	0.0339	0.0245	0.0563	0.0353

*For female breast cancer multiply by female population and for prostate cancer multiply by male population.

Note: These calculations provide only a rough approximation of the number of people in a specific community who may develop or die of cancer. These estimates should be used with caution because they do not reflect the age or racial characteristics of the population, access to detection and treatment, or exposure to risk factors. State cancer registries count the number of cancers that occur in localities throughout the state. The American Cancer Society recommends using data from these registries, when it is available, to more accurately estimate local cancer statistics.

Source: DEVCAN Software, Version 4.0, Surveillance, Epidemiology, and End Results Program, 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute. American Cancer Society, Surveillance Research

- Non-Hodgkin's lymphomas (4.0%) and Hodgkin's disease (4.4%), cancers that involve the lymph nodes, but also may invade bone marrow and other organs. They may cause swelling of lymph nodes in the neck, armpit, or groin. Other symptoms may include general weakness and fever.
- Retinoblastoma (3.1%), an eye cancer, usually occurs in children under age 4. When detected early, cure is possible with appropriate treatment.
- Wilms' tumor (6.1%), a kidney cancer, may be recognized by a swelling or lump in the abdomen.

Treatment: Childhood cancers can be treated by a combination of therapies chosen based on the specific type and stage of the cancer. Treatment is coordinated by a team of experts including oncologic physicians, pediatric nurses, social workers, psychologists, and others who assist children and their families.

Survival: Five-year survival rates vary considerably, depending on the site: all sites, 75%; bone cancer, 67%; neuroblastoma, 71%; brain and central nervous system, 64%; Wilms' tumor (kidney), 93%; Hodgkin's disease, 93%; and acute lymphocytic leukemia, 81%.

COLON AND RECTUM

New Cases: An estimated 130,200 cases in 2000, including 93,800 of colon cancer and 36,400 of rectal cancer. Colorectal cancers are the third most common cancers in men and women. Incidence rates declined significantly during 1992–1996 (-2.1% per year). Research suggests that these declines may be due to increased screening and polyp removal, preventing progression of polyps to invasive cancers.

Deaths: An estimated 56,300 deaths (47,700 from colon cancer, 8,600 from rectal cancer) in 2000, accounting for about 11% of cancer deaths. Mortality rates for colorectal cancer have also declined for men and women over the past 20 years. This decrease probably reflects the decreasing trends in incidence rates and the increasing survival rates.

Signs and Symptoms: Rectal bleeding, blood in the stool, a change in bowel habits.

Risk Factors: A personal or family history of colorectal cancer or polyps, and inflammatory bowel disease have been associated with increased colorectal cancer risk. Other possible risk factors include physical inactivity, high-fat and/or low-fiber diet, as well as inadequate intake of fruits and vegetables. Recent studies have suggested that estrogen replacement therapy and nonsteroidal antiinflammatory drugs such as aspirin may reduce colorectal cancer risk.

Early Detection: Beginning at age 50, men and women should have one of the following: a fecal occult blood test (FOBT) and flexible sigmoidoscopy (if normal, repeat FOBT annually, and flexible sigmoidoscopy every 5 years), or colonoscopy (if normal, repeat every 10 years), or double-contrast barium enema (if normal, repeat every 5 to 10 years). A digital rectal examination should be done at the same time as sigmoidoscopy, colonoscopy, or double-contrast barium enema. These tests offer the best opportunity to detect colorectal cancer at an early stage when successful treatment is likely, and to prevent some cancers by detection and removal of polyps.

People should begin colorectal cancer screening earlier and/or undergo screening more often if they have a personal history of colorectal cancer or adenomatous polyps, a strong family history of colorectal cancer or polyps, a personal history of chronic inflammatory bowel disease, or if they are a member of a family with hereditary colorectal cancer syndromes.

Treatment: Surgery is the most common form of therapy for colorectal cancer, and for cancers that have not spread, it is frequently curative. Chemotherapy, or

Probability of Developing Invasive Cancers Over Selected Age Intervals, by Sex, United States, 1994–1996*

		Birth to 39 (%)	40 to 59 (%)	60 to 79 (%)	Birth to Death (%)
All sites†	Male	1.61 (1 in 62)	8.17 (1 in 12)	33.65 (1 in 3)	43.56 (1 in 2)
	Female	1.94 (1 in 52)	9.23 (1 in 11)	22.27 (1 in 4)	38.11 (1 in 3)
Breast	Female	0.43 (1 in 235)	4.06 (1 in 25)	6.88 (1 in 15)	12.56 (1 in 8)
Colon & Rectum	Male	0.06 (1 in 1,579)	0.85 (1 in 124)	3.97 (1 in 29)	5.64 (1 in 18)
	Female	0.05 (1 in 1,947)	0.67 (1 in 149)	3.06 (1 in 33)	5.55 (1 in 18)
Lung & Bronchus	Male	0.04 (1 in 2,592)	1.29 (1 in 78)	6.35 (1 in 16)	8.11 (1 in 12)
	Female	0.03 (1 in 2,894)	0.94 (1 in 106)	3.98 (1 in 25)	5.69 (1 in 18)
Prostate	Male	Less than 1 in 10,000	1.90 (1 in 53)	13.69 (1 in 7)	15.91 (1 in 6)

*Of those free of cancer at beginning of age interval. Based on cancer cases diagnosed during 1994–1996. The "1 in" statistic and the inverse of the percentage may not be equivalent due to rounding.
†Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: DEVCAN Software, Version 4.0, Surveillance, Epidemiology, and End Results Program, 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute. American Cancer Society, Surveillance Research

chemotherapy plus radiation is given before or after surgery to most patients whose cancer has deeply perforated the bowel wall or has spread to the lymph nodes. A permanent colostomy (creation of an abdominal opening for elimination of body wastes) is seldom needed for colon cancer and is infrequently required for rectal cancer.

Survival: The 1- and 5-year relative survival rates for patients with colon and rectum cancer are 80% and 61%, respectively. When colorectal cancers are detected in an early, localized stage, the 5-year relative survival rate is 90%; however, only 37% of colorectal cancers are discovered at that stage. After the cancer has spread regionally to involve adjacent organs or lymph nodes, the rate drops to 65%. The 5-year survival rate for persons with distant metastases is 8%. Survival continues to decline beyond five years, and 54% of persons diagnosed with colorectal cancers survive 10 years.

LEUKEMIA

New Cases: An estimated 30,800 new cases in 2000, approximately evenly divided between acute leukemia and chronic leukemia. Although often thought of as primarily a childhood disease, leukemia is expected to strike many more adults (28,200) than children (2,600) this year. Acute lymphocytic leukemia accounts for approximately 1,800 of the leukemia cases among children. In adults, the most common types are acute myeloid (approximately 9,700 cases) and chronic lymphocytic (approximately 8,100 cases).

Deaths: An estimated 21,700 deaths in 2000.

Signs and Symptoms: Fatigue, paleness, weight loss, repeated infections, bruising easily, and nosebleeds or other hemorrhages. In children, these signs can appear suddenly. Chronic leukemia can progress slowly and with few symptoms.

Risk Factors: Leukemia strikes both sexes and all ages. Causes of most leukemias are unknown. Persons with Down syndrome and certain other genetic abnormalities have higher incidence rates of leukemia. It has also been linked to excessive exposure to ionizing radiation and to certain chemicals such as benzene, a commercially used toxic liquid that is also present in lead-free gasoline. Certain forms of leukemia and lymphoma are caused by a retrovirus, human T-cell leukemia/lymphoma virus-I (HTLV-I).

Early Detection: Because symptoms often resemble those of other, less serious conditions, leukemia can be difficult to diagnose early. When a physician does suspect leukemia, diagnosis can be made using blood tests and bone marrow biopsy.

Treatment: Chemotherapy is the most effective method of treating leukemia. Various anticancer drugs are used, either in combinations or as single agents. Transfusions of blood components and antibiotics are used as supportive treatments. Under appropriate conditions, bone marrow transplantation may be useful in treating certain leukemias.

Survival: The 1-year relative survival rate for patients with leukemia is 64%. Survival drops to 43% five years after diagnosis, primarily due to the poor survival of patients with some types of leukemia, such as acute myelocytic. There has been a dramatic improvement in survival for patients with acute lymphocytic leukemia—from a 5-year relative survival rate of 38% in the mid-1970s to 59% in the early 1990s. Survival rates for children have increased from 53% to 81% over the same time period.

LUNG AND BRONCHUS

New Cases: An estimated 164,100 new cases in 2000, accounting for 14% of cancer diagnoses. The incidence

rate is declining significantly in men, from a high of 86.5 per 100,000 in 1984 to 70.0 in 1996. In the 1990s, the rate of increase among women began to slow. In 1996, the incidence rate in women was 42.3 per 100,000.

Deaths: An estimated 156,900 deaths in 2000, accounting for 28% of all cancer deaths. During 1992–1996, mortality from lung cancer declined significantly among men (-1.7% per year) while rates for women were still significantly increasing (0.9% per year). Since 1987, more women have died each year of lung cancer than breast cancer, which, for over 40 years, was the major cause of cancer death in women. Decreasing lung cancer incidence and mortality rates most likely result from decreased smoking rates over the previous 30 years. However, decreasing smoking patterns among women lag behind those of men. Of concern, the declines in adult tobacco use have slowed, and tobacco use in youth is increasing again.

Signs and Symptoms: Persistent cough, sputum streaked with blood, chest pain, and recurring pneumonia or bronchitis.

Risk Factors: Cigarette smoking is by far the most important risk factor in the development of lung cancer. Other risk factors include exposure to certain industrial substances, such as arsenic; some organic chemicals; radon and asbestos, particularly for persons who smoke; radiation exposure from occupational, medical, and environmental sources; air pollution; tuberculosis; and environmental tobacco smoke in nonsmokers.

Early Detection: Because symptoms often do not appear until the disease is advanced, early detection is difficult. In those who stop smoking when precancerous changes are found, damaged lung tissue often returns to normal. Chest x-ray, analysis of cells contained in sputum, and fiberoptic examination of the bronchial passages assist in diagnosis.

Treatment: Treatment options are determined by the type and stage of the cancer and include surgery, radiation therapy, and chemotherapy. For many localized cancers, surgery is usually the treatment of choice. Because the disease has usually spread by the time it is discovered, radiation therapy and chemotherapy are often needed in combination with surgery. Chemotherapy alone or combined with radiation is the treatment of choice for small cell lung cancer; on this regimen, a large percentage of patients experience remission, which in some cases is long-lasting.

Survival: The 1-year relative survival rates for lung cancer have increased from 34% in 1975 to 41% in 1995, largely due to improvements in surgical techniques. The 5-year relative survival rate for all stages combined is only 14%. The survival rate is 49% for cases detected when the disease is still localized, but only 15% of lung cancers are discovered that early.

LYMPHOMA

New Cases: An estimated 62,300 new cases in 2000, including 7,400 cases of Hodgkin's disease and 54,900 cases of non-Hodgkin's lymphoma. Since the early 1970s, incidence rates for non-Hodgkin's lymphoma have nearly doubled; during the 1990s, the rate of increase appeared to slow and may be beginning to decline. Incidence rates for Hodgkin's disease have declined over the past two decades, particularly among the elderly.

Deaths: An estimated 27,500 deaths in 2000 (non-Hodgkin's lymphoma, 26,100; Hodgkin's disease, 1,400).

Signs and Symptoms: Enlarged lymph nodes, itching, fever, night sweats, anemia, and weight loss. Fever can come and go in periods of several days or weeks.

Risk Factors: Risk factors are largely unknown but in part involve reduced immune function and exposure to certain infectious agents. Persons with organ transplants are at higher risk due to altered immune function. Human immunodeficiency virus (HIV) and human T-cell leukemia/lymphoma virus-I (HTLV-I) are associated with increased risk of non-Hodgkin's lymphoma. Burkitt's lymphoma in Africa is partly caused by the Epstein-Barr virus. Other possible risk factors include occupational exposures to herbicides and perhaps other chemicals.

Treatment: Hodgkin's disease: chemotherapy and radiotherapy are useful for most patients. Non-Hodgkin's lymphoma: early stage, localized lymph node disease can be treated with radiotherapy. Patients with later-stage disease are treated with chemotherapy or with chemotherapy plus radiation depending on the specific type of non-Hodgkin's lymphoma. New treatment programs using highly specific monoclonal antibodies directed at lymphoma cells, and high-dose chemotherapy with bone marrow transplantation, are being tested in selected patients who relapsed after standard treatment.

Survival: Survival rates vary widely by cell type and stage of disease. The 1-year relative survival rates for Hodgkin's and non-Hodgkin's lymphoma are 93% and 70%, respectively; the 5-year rates are 82% and 51%. Ten years after diagnosis, the relative survival rates for Hodgkin's and non-Hodgkin's disease decline to 72% and 41%; and the 15-year survival rates are 63% and 35%, respectively.

ORAL CAVITY AND PHARYNX

New Cases: An estimated 30,200 new cases in 2000. Incidence rates are more than twice as high in men as in

women and are greatest in men who are over age 40. During 1992–1996, the rates of oral cancers were declining.

Deaths: An estimated 7,800 deaths in 2000. Mortality rates have been decreasing since the early 1980s.

Signs and Symptoms: A sore that bleeds easily and does not heal; a lump or thickening; a red or white patch that persists. Difficulty in chewing, swallowing, or moving tongue or jaws are often late symptoms.

Risk Factors: Cigarette, cigar, or pipe smoking; use of smokeless tobacco; excessive consumption of alcohol.

Early Detection: Cancer can affect any part of the oral cavity, including the lip, tongue, mouth, and throat. Dentists and primary care physicians have the opportunity, during regular checkups, to see abnormal tissue changes and to detect cancer at an early, curable stage.

Treatment: Radiation therapy and surgery are standard treatments. In advanced disease, chemotherapy may be useful as an adjunct to surgery.

Survival: Eighty-two percent of oral cavity and pharynx cancer patients survive one year after diagnosis. For all stages combined, the 5-year relative survival rate is 53%; and the 10-year rate is 43%.

OVARY

New Cases: An estimated 23,100 new cases in the United States in 2000. It accounts for 4% of all cancers among women and ranks second among gynecologic cancers. During 1992–1996, ovarian cancer incidence rates were significantly declining.

Deaths: An estimated 14,000 deaths in 2000. Ovarian cancer causes more deaths than any other cancer of the female reproductive system.

Signs and Symptoms: Ovarian cancer often does not show any obvious signs or symptoms until late in its development. The most common sign is enlargement of the abdomen, which is caused by accumulation of fluid. Abnormal vaginal bleeding is rarely a symptom. In women over 40, vague digestive disturbances (stomach discomfort, gas, distention) that persist and cannot be explained by any other cause may indicate the need for an evaluation for ovarian cancer, including a thorough pelvic examination.

Risk Factors: Risk for ovarian cancer increases with age and peaks in the eighth decade. Women who have never had children are more likely to develop ovarian cancer than those who have. Pregnancy and the use of oral contraceptives appear to reduce the risk of developing ovarian cancer. Women who have had breast cancer or have a family history of breast or ovarian cancer are at increased risk. Mutations in BRCA1 or BRCA2 have been observed in these families. Another genetic syndrome, hereditary non-polyposis colon cancer, also has been associated with endometrial and ovarian cancer. Except for Japan, industrialized countries have the highest incidence rates.

Early Detection: Periodic, thorough pelvic exams are important. The Pap test, useful in detecting cervical cancer, rarely uncovers early ovarian cancer. Transvaginal ultrasound and a tumor marker, CA125, may assist diagnosis but are not used for routine screening.

Treatment: Surgery, radiation therapy, and chemotherapy are treatment options. Surgery usually includes the removal of one or both ovaries, the fallopian tubes (salpingo-oophorectomy), and the uterus (hysterectomy). In some very early tumors, only the involved ovary will be removed, especially in young women who wish to have children. In advanced disease, an attempt is made to remove all intraabdominal disease to enhance the effect of chemotherapy.

Survival: Seventy-eight percent of ovarian cancer patients survive one year after diagnosis; the 5-year relative survival rate for all stages is 50%. If diagnosed and treated early, the rate is 95%; however, only about 25% of all cases are detected at the localized stage. Five-year relative survival rates for women with regional and distant disease are 79% and 28%, respectively.

PANCREAS

New Cases: An estimated 28,300 new cases in the United States in 2000. Over the past 20 years, rates of pancreatic cancer have declined in men. Rates among women have remained approximately constant but may be beginning to decline.

Deaths: An estimated 28,200 deaths in 2000. Over the past 20 years, there has been a slight but significant decrease in mortality rates among men (about –0.9% per year) while rates have increased slightly among women.

Signs and Symptoms: Cancer of the pancreas generally occurs without symptoms until it is in advanced stages. If a cancer develops in an area of the pancreas near the common bile duct, its blockage may lead to jaundice (a noticeable yellowing of the skin due to pigment accumulation). Sometimes this symptom allows the tumor to be diagnosed at an early stage.

Risk Factors: Very little is known about what causes the disease or how to prevent it. Risk increases with age, and smoking is a risk factor. Incidence rates are more than twice as high for smokers as for nonsmokers. Some studies have suggested associations with chronic pancreatitis, diabetes, and cirrhosis. Pancreatic cancer rates are higher in countries with a diet high in fat.

Five-Year Relative Survival Rates* by Stage at Diagnosis, 1989-1995

Site	All Stages %	Local %	Regional %	Distant %	Site	All Stages %	Local %	Regional %	Distant %
Breast (female)	85	96	77	21	Ovary	50	95	79	28
Colon & rectum	61	90	65	8	Pancreas	4	18	6	1
Esophagus	12	25	13	2	Prostate†	92	100	—	32
Kidney	60	88	61	10	Stomach	21	60	21	2
Larynx	65	81	53	41	Testis	95	99	97	74
Liver	5	15	5	1	Thyroid	95	100	92	43
Lung & bronchus	14	49	20	2	Urinary bladder	81	93	49	6
Melanoma	88	95	58	13	Uterine cervix	70	91	48	13
Oral	53	81	43	22	Uterine corpus	84	95	64	25

*Rates are adjusted for normal life expectancy and are based on cases diagnosed from 1989-1995, followed through 1996.
†The rate for local stage represents local and regional stages combined.

Local: An invasive malignant cancer confined entirely to the organ of origin. **Regional:** A malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes by way of lymphatic system; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** A malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

Source: Surveillance, Epidemiology, and End Results Program, 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute. American Cancer Society, Surveillance Research

Early Detection: At present, only biopsy yields a certain diagnosis, and because of the "silent" course of the disease, the need for biopsy is likely to be obvious only after the disease has advanced. Researchers are focusing on ways to diagnose pancreatic cancer before symptoms occur.

Treatment: Surgery, radiation therapy, and chemotherapy are treatment options that can extend survival and/or relieve symptoms in many patients but are not likely to produce a cure for most. Clinical trials with several new agents may offer improved survival and should be considered an option.

Survival: For all stages combined, the 1-year relative survival rate is only 19%, and the 5-year rate is 4%.

PROSTATE

New Cases: An estimated 180,400 new cases in the US during 2000. Prostate cancer incidence rates remain significantly higher in black men than in white men. Between 1989 and 1992, prostate cancer incidence rates increased dramatically, probably due to earlier diagnosis in men without any symptoms, by increased use of prostate-specific antigen (PSA) blood test screenings. Prostate cancer incidence rates are now declining; rates peaked in 1992 among white men and in 1993 among black men.

Deaths: An estimated 31,900 deaths in 2000, the second leading cause of cancer death in men. During 1992–1996, prostate cancer mortality rates declined significantly (–2.5% per year). Although mortality rates are declining among white and black men, rates in black men remain more than twice as high as rates in white men.

Signs and Symptoms: Weak or interrupted urine flow; inability to urinate, or difficulty starting or stopping the urine flow; the need to urinate frequently, especially at night; blood in the urine; pain or burning on urination; continual pain in lower back, pelvis, or upper thighs. Most of these symptoms are nonspecific and may be similar to those caused by benign conditions such as infection or prostate enlargement.

Risk Factors: The incidence of prostate cancer increases with age; more than 75% of all prostate cancers are diagnosed in men over age 65. Black Americans have the highest prostate cancer incidence rates in the world; the disease is common in North America and Northwestern Europe and is rare in Asia, Africa, and South America. Recent genetic studies suggest that strong familial predisposition may be responsible for 5%-10% of prostate cancers. International studies suggest that dietary fat may also be a factor.

Early Detection: Men age 50 and older who have at least a 10-year life expectancy should talk with their health care professional about having a digital rectal exam of the prostate gland and a prostate-specific antigen (PSA) blood test every year. Men who are at high risk for prostate cancer (black men or men who have a history of prostate cancer in close family members) should consider beginning these tests at an earlier age.

Treatment: Depending on age, stage of the cancer, and other medical conditions of the patient, surgery and radiation should be discussed with the patient's physicians. Hormones and chemotherapy or combinations of these options might be considered for metastatic disease. Hormone treatment may control prostate cancer for long

periods by shrinking the size of the tumor, thus relieving pain and other symptoms. Careful observation without immediate active treatment ("watchful waiting") may be appropriate, particularly for older individuals with low-grade and/or early stage tumors.

Survival: Seventy-nine percent of all prostate cancers are discovered in the local and regional stages; the 5-year relative survival rate for patients whose tumors are diagnosed at these stages is 100%. Over the past 20 years, the survival rate for all stages combined has increased from 67% to 92%. Survival after a diagnosis of prostate cancer continues to decline beyond five years. According to the most recent data, 67% of men diagnosed with prostate cancer survive 10 years and 52% survive 15 years.

SKIN

New Cases: Approximately 1.3 million cases a year of highly curable basal cell or squamous cell cancers. They are more common among individuals with lightly pigmented skin. The most serious form of skin cancer is melanoma, which is expected to be diagnosed in about 47,700 persons in 2000. Since the early 1970s, the incidence rate of melanoma has increased significantly on average 4% per year from 5.7 per 100,000 in 1973 to 13.8 in 1996. Incidence rates are more than 10 times higher in whites than in blacks. Other important skin cancers include Kaposi's sarcoma and cutaneous T-cell lymphoma.

Deaths: An estimated 9,600 deaths this year, 7,700 from melanoma and 1,900 from other skin cancers.

Signs and Symptoms: Any change on the skin, especially a change in the size or color of a mole or other darkly pigmented growth or spot. Scaliness, oozing, bleeding, or change in the appearance of a bump or nodule, the spread of pigmentation beyond its border, a change in sensation, itchiness, tenderness, or pain.

Risk Factors: Excessive exposure to ultraviolet radiation; fair complexion; occupational exposure to coal tar, pitch, creosote, arsenic compounds, or radium; family history; and multiple nevi (moles) or atypical nevi.

Prevention: The sun's ultraviolet rays are strongest during the midday hours (10 a.m.-4 p.m.); exposure at these times should be limited or avoided. When outdoors, cover as much skin as possible with a hat that shades the face, neck, and ears, and a long-sleeved shirt and long pants. Sunscreen comes in various strengths, graded by the solar protection factor (SPF). Use a sunscreen with an SPF of 15 or higher. Because of the possible link between severe sunburns in childhood and greatly increased risk of melanoma in later life, children, in particular, should be protected from the sun.

Early Detection: Early detection is critical. Recognition of changes in skin growths or the appearance of new growths is the best way to find early skin cancer. Adults should practice skin self-exam regularly. Suspicious lesions should be evaluated promptly by a physician. Basal and squamous cell skin cancers often take the form of a pale, waxlike, pearly nodule, or a red, scaly, sharply outlined patch. A sudden or progressive change in a mole's appearance should be checked by a physician. Melanomas often start as small, mole-like growths that increase in size and change color. A simple **ABCD** rule outlines the warning signals of melanoma: **A** is for asymmetry. One half of the mole does not match the other half. **B** is for border irregularity. The edges are ragged, notched, or blurred. **C** is for color. The pigmentation is not uniform, with variable degrees of tan, brown, or black. **D** is for diameter greater than 6 millimeters. Any sudden or progressive increase in size should be of particular concern.

Treatment: There are five methods of treatment for basal cell cancer and squamous cell cancer: surgery (used in 90% of cases), radiation therapy, electrodessication (tissue destruction by heat), cryosurgery (tissue destruction by freezing), and laser therapy for early skin cancer. For malignant melanoma, the primary growth must be adequately excised, and it may be necessary to remove nearby lymph nodes. Removal and microscopic examination of all suspicious moles is essential. Advanced cases of melanoma are treated with radiation therapy, immunotherapy, or chemotherapy according to the characteristics of the case.

Survival: For basal cell or squamous cell cancers, cure is highly likely if detected and treated early. Malignant melanoma can spread to other parts of the body quickly; however, when detected in its earliest stages, and with proper treatment, it is highly curable. The 5-year relative survival rate for patients with malignant melanoma is 88%. For localized malignant melanoma, the 5-year relative survival rate is 95%; and rates for regional and distant disease are 58% and 13%, respectively. About 82% of melanomas are diagnosed at a localized stage.

URINARY BLADDER

New Cases: An estimated 53,200 new cases in 2000. Bladder cancer incidence rates are significantly declining in the 1990s. Overall, bladder cancer incidence is about four times higher in men than in women, and two times higher in whites than in blacks.

Deaths: An estimated 12,200 deaths in 2000. Since the early 1970s, mortality rates for bladder cancer have decreased significantly in both whites and blacks.

Trends in 5-Year Relative Survival Rates* by Race and Year of Diagnosis, United States, 1974–1995

	White			Black			All Races		
	Relative 5-Year Survival Rate (%)			Relative 5-Year Survival Rate (%)			Relative 5-Year Survival Rate (%)		
Site	1974-76	1980-82	1989-95	1974-76	1980-82	1989-95	1974-76	1980-82	1989-95
All Sites	51	52	61†	39	40	48†	50	51	59†
Brain	22	25	30†	27	31	39†	22	25	30†
Breast (female)	75	77	86†	63	66	71†	75	76	85†
Colon	51	56	62†	46	49	52†	50	55	62†
Esophagus	5	7	13†	4	5	9†	5	7	12†
Hodgkin's disease	72	75	83†	69	72	76	71	75	82†
Kidney	52	51	61†	49	55	58†	52	52	60†
Larynx	66	69	66	60	58	53	66	68	65
Leukemia	35	39	44†	31	33	34	34	39	43†
Liver	4	4	6†	2	2	3	4	4	5†
Lung & bronchus	13	14	14†	12	12	11	13	13	14†
Melanoma	80	83	88†	67‡	61§	68‡	80	83	88†
Multiple myeloma	24	28	28†	28	29	31	24	28	28†
Non-Hodgkin's lymphoma	48	52	52†	48	50	41†	47	51	51†
Oral cavity	55	55	56	36	31	34	53	53	53
Ovary	37	39	50†	41	39	47†	37	39	50†
Pancreas	3	3	4†	3	5	4†	3	3	4†
Prostate	68	75	93†	58	65	84†	67	73	92†
Rectum	49	53	60†	42	38	51†	49	52	60†
Stomach	15	17	19†	17	19	22	15	18	21†
Testis	79	92	96†	76‡	90‡	88	79	92	95†
Thyroid	92	94	95†	88	94	89	92	94	95†
Urinary bladder	74	79	82†	48	58	62†	73	78	81†
Uterine cervix	70	68	71†	64	61	59	69	67	70
Uterine corpus	89	83	86†	61	54	56	88	82	84†

*Rates are adjusted for normal life expectancy and are based on cases diagnosed from 1989-1995, followed through 1996.

†The difference in rates between 1974-76 and 1989-95 is statistically significant ($p < 0.05$).

‡The standard error of the survival rate is between 5 and 10 percentage points.

§The standard error of the survival rate is greater than 10 percentage points.

Source: Surveillance, Epidemiology, and End Results Program, 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute.
American Cancer Society, Surveillance Research

Signs and Symptoms: Blood in the urine; usually associated with increased frequency of urination.

Risk Factors: Smoking is the greatest risk factor for bladder cancer, with smokers experiencing twice the risk of nonsmokers. Smoking is estimated to be responsible for about 47% of bladder cancer deaths among men and 37% among women. People living in urban areas and workers in dye, rubber, or leather industries also have a higher risk.

Early Detection: Bladder cancer is diagnosed by examination of cells in the urine and examination of the bladder wall with a cystoscope, a slender tube fitted with a lens and light that can be inserted into the tract through the urethra.

Treatment: Surgery, alone or in combination with other treatments, is used in more than 90% of cases. Superficial, localized cancers may be treated by administering immunotherapy or chemotherapy directly into the bladder. Chemotherapy alone or with radiation before cystectomy (bladder removal) has improved some treatment results.

Survival: When diagnosed at a localized stage, the 5-year relative survival rate is 93%; 73% of cancers are detected this early. For regional and distant stage, 5-year relative survival rates are 49% and 6%, respectively. Beyond five years, survival continues to decline with 75% of patients surviving 10 years after diagnosis, and 68% surviving 15 years.

Uterine Cervix

New Cases: An estimated 12,800 cases of invasive cervical cancer are expected to be diagnosed in 2000. Incidence rates have decreased steadily over the past several decades. In 1992–1996, the incidence rate in

black women (11.2 per 100,000) was higher than the rate in white women (7.3 per 100,000). As Pap screening has become more prevalent, carcinoma in situ of the cervix occurs more frequently than invasive cancer.

Deaths: An estimated 4,600 cervical cancer deaths in 2000. Mortality rates have also declined sharply over the past several decades. During 1992–1996, cervical cancer mortality rates declined on average about −2.1% per year.

Signs and Symptoms: Abnormal vaginal bleeding or spotting; abnormal vaginal discharge. Pain and systemic symptoms are late manifestations of the disease.

Risk Factors: Cervical cancer risk is closely linked to sexual behavior and to sexually transmitted infections with certain types of human papillomavirus. Women who have sex at an early age, many sexual partners, or have partners who have had many sexual partners are at higher risk of developing the disease. Other risk factors include cigarette smoking and low socioeconomic status.

Early Detection: The Pap test is a simple procedure that can be performed by a health care professional as part of a pelvic exam. A small sample of cells is swabbed from the cervix, transferred to a slide, and examined under a microscope. This test should be performed annually with a pelvic exam in women who are, or have been, sexually active or who have reached age 18. After three or more consecutive annual exams with normal findings, the Pap test may be performed less frequently at the discretion of the physician.

Treatment: Invasive cervical cancers generally are treated by surgery or radiation, or both. For in situ cancers, changes in the cervix may be treated by cryotherapy (the destruction of cells by extreme cold), by electrocoagulation (the destruction of tissue through intense heat by electric current), laser ablation, or by local surgery.

Survival: Eighty-nine percent of cervical cancer patients survive one year after diagnosis, and 70% survive five years. When detected at an early stage, invasive cervical cancer is one of the most successfully treatable cancers with a 5-year relative survival rate of 91% for localized cancers. Whites are more likely than blacks to have their cancers diagnosed at this early stage. Fifty-five percent of cervical cancers in white women and 44% of cancers in black women are diagnosed at a localized stage.

Uterine Corpus (Endometrium)

New Cases: An estimated 36,100 cases of cancer of the uterine corpus (body of the uterus), usually of the endometrium or lining of the uterus, are expected to be diagnosed in 2000. Incidence rates are higher among white women (22.4 per 100,000) than among black women (15.3 per 100,000).

Deaths: An estimated 6,500 deaths in 2000. Although incidence rates are higher among white women than black women, the relationship is reversed for mortality rates—black women have mortality rates that are nearly twice as high as those among white women.

Signs and Symptoms: Abnormal uterine bleeding or spotting. Pain and systemic symptoms are late manifestations of the disease.

Risk Factors: Estrogen is the major risk factor for the most common type of cancer of the uterine corpus. Estrogen-related exposures including estrogen replacement therapy, tamoxifen, early menarche, late menopause, never having children, and a history of failure to ovulate have all been shown to increase risk. Progesterone plus estrogen replacement therapy (called hormone replacement therapy) is believed to largely offset the increased risk related to using only estrogen. Research has not implicated estrogen exposures in the development of the other types of endometrial cancer, which are more aggressive and have a poorer prognosis. Other risk factors for uterine corpus cancer include infertility, diabetes, gallbladder disease, hypertension, and obesity. Pregnancy and the use of oral contraceptives appear to provide protection against endometrial cancer. Hereditary non-polyposis colon cancer, a genetic syndrome, also has been associated with endometrial and ovarian cancer.

Early Detection: The Pap test, highly effective in detecting early cancer of the cervix, is rarely effective in detecting early endometrial cancer. Women 40 and over should have an annual pelvic exam by a health care professional. Endometrial biopsy is recommended at menopause and periodically thereafter for women at very high risk of developing endometrial cancer although the frequency of biopsy is at the discretion of the physician.

Treatment: Uterine cancers are usually treated with surgery, radiation, hormones, and/or chemotherapy depending on the stage of disease.

Survival: The 1-year relative survival rate for endometrial cancer is 93%. The 5-year relative survival rate is 95% if the cancer is discovered at an early stage and 64% if diagnosed at a regional stage. Relative survival rates for whites exceed those for blacks by at least 18% at every stage.

SPECIAL SECTION: CHILDHOOD CANCER

Introduction

Children and young persons under the age of 20 comprise almost 30% of the US population. Although cancer occurs rarely at these ages, an estimated 12,400 children and young people will be diagnosed with cancer in the year 2000. Despite steady advances in treatment, 2,300 children will die of cancer in the year 2000. While cancer is only a minor cause of death in infancy (<1 year), it was the third most common cause of death between the ages of 1 and 19 in 1997, following unintentional injuries and homicides. It constitutes about 8% of deaths between age 1 and 19, and is the leading cause of death from disease at these ages.

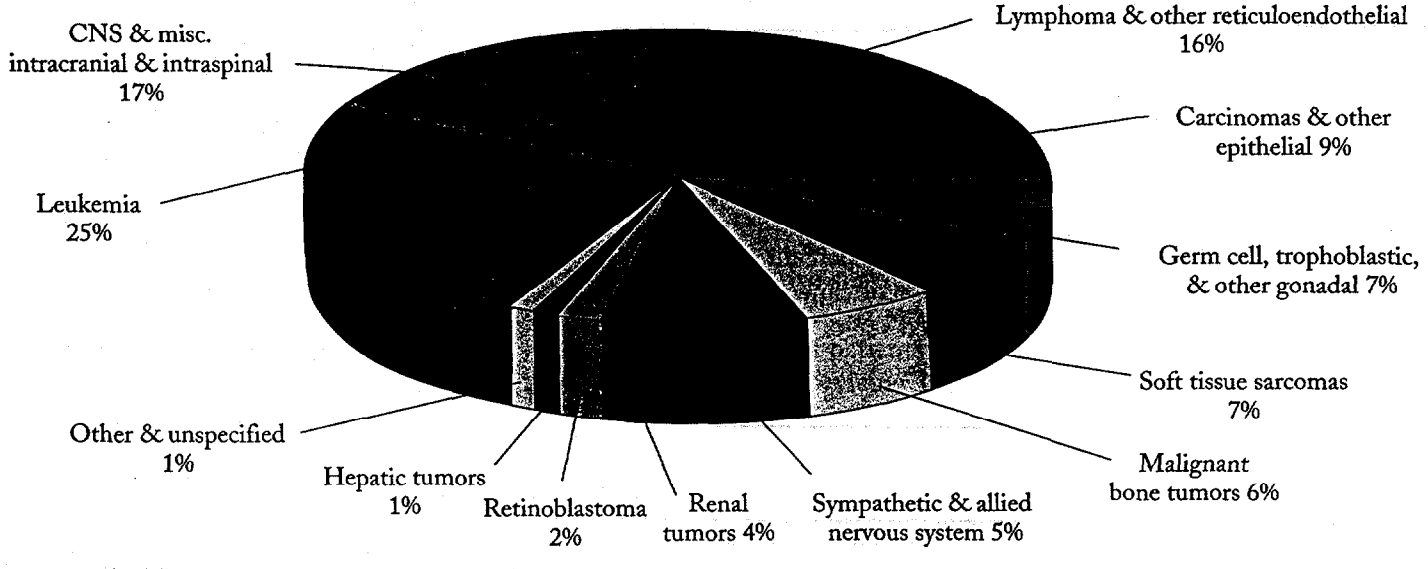
While cancers among adults are categorized by the anatomical site of the primary tumor, childhood cancers are classified primarily by histology into 12 major categories using the International Classification of Childhood Cancers (ICCC).[1,2] Studying all childhood cancers combined provides insight into the overall burden of cancer in children. However, there are important differences among childhood cancer categories. Figure 1 presents the distribution of childhood cancers by ICCC category.[2]

Trends over time: The incidence rate of all childhood cancers combined increased from the early 1970s—when rates were first measured by the SEER program of the National Cancer Institute—until 1991 and then leveled off and declined slightly through 1996 (Figure 2).[2,3] Incidence rates by 5-year calendar period for different categories of childhood cancer combined can be seen in Figure 3.[3] Small increases in the incidence of several childhood cancer types, including central nervous system (CNS) tumors, leukemias, and some neuroblastomas have been attributed to changes in diagnostic technology, reporting, and classification.[4] Similarly, observed increases in cancers among infants (age < 1 year) may be due to earlier diagnosis and better case identification rather than a true increase in the incidence of cancer in infants.[2] Reasons for modest increases in retinoblastomas and small declines in Hodgkin's disease remain unclear.[4]

Mortality rates from all childhood cancers combined decreased steadily from 1975 to 1996 (Figure 2).[2,3] This decrease results from improvements in survival for most childhood cancers (Figure 4).[2] The overall 5-year relative survival rate for cancers diagnosed before age 20 has risen to 74.9%, and 10-year survival is approaching 70%.[3] Survival does not decrease considerably beyond 10 years after diagnosis, since the loss of life from childhood cancer is greatest in the first few years after diagnosis.[3]

The largest impact on these trends has been from dramatic improvement in survival from leukemia, which accounts for almost one-third of all cancers in children under age 15, and one-fourth of all cancers under age 20. The availability of newer, more effective chemotherapy treatments is the principal cause of improved survival among childhood cancer patients.[2]

Figure 1. Distribution of Childhood Cancers (Age 0–19) by ICCC Category, 1975–1995



Source: *Pediatric Monograph* 1999, Surveillance, Epidemiology, and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

Age: Incidence rates for all sites combined are highest among infants, decline until age 9, and then rise again with increasing age. When incidence is grouped by 5-year age categories, rates are highest among ages 0–4 and 15–19 and lowest among children aged 5–9.[2] However, the association between age and childhood cancer incidence varies by cancer site (Figure 5).[5]

Gender: The overall cancer incidence rate is higher for boys than for girls (Figure 6), although the nature of this relationship varies by cancer type and age.[3, 6]

Race/Ethnicity: Based on data from 1992-1996, overall childhood cancer incidence was highest among whites, intermediate among Hispanics, Asian/Pacific Islanders, and blacks, and lowest among American Indians/Alaska Natives (Figure 6).[6]

Categories of Childhood Cancer

The following are the 12 major categories of the ICCC:

Leukemia: Leukemia is the most common form of cancer in childhood, affecting approximately 2,600 children under age 15 in the United States each year. Leukemia accounts for about one-third of all cancers in children under age 15 and about one-fourth of all cancers occurring before age 20.[7]

Acute lymphoblastic leukemia (ALL) constitutes approximately three-fourths of all childhood leukemias. The peak occurrence of ALL is between ages 2 and 3, with rates slightly higher among whites and males. Five-year relative survival from ALL has greatly increased over time, and is now nearly 80%, primarily due to several improvements in treatment.[7] Survival from ALL is quite dependent on age at diagnosis, with poorer survival among infants and among children aged 10 and older.[7] Other prognostic factors include the white blood cell count, immune surface markers on the leukemia cells, and presence of certain chromosome changes.

Acute myeloid leukemia (AML) is responsible for much of the remainder of childhood leukemia. AML incidence rates are highest in the first two years of life, and increase once again in later childhood. Incidence rates are similar for whites and blacks.[7] Five-year survival from AML has also improved over time, but at just over 40%, remains substantially lower than ALL survival.[3]

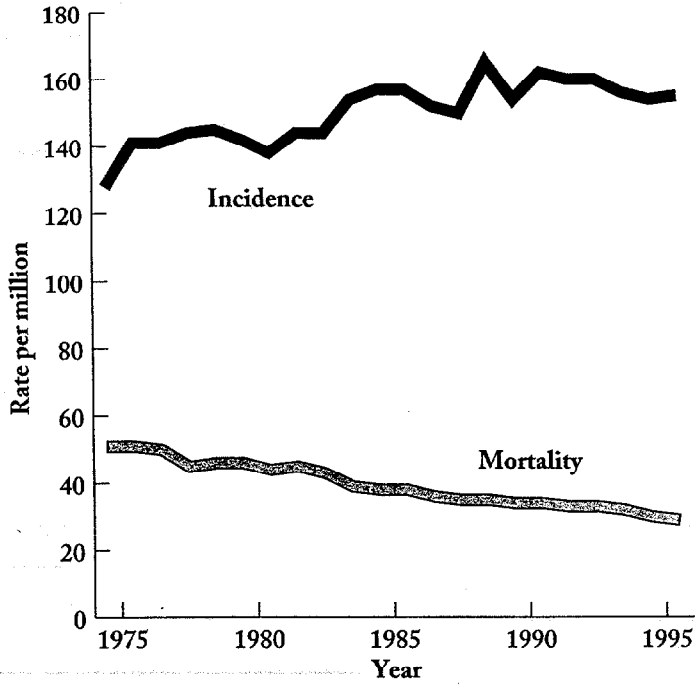
Lymphomas and Other Reticuloendothelial Neoplasms: Lymphomas are the third most common form of childhood cancer, accounting for more than 10% of cases among children under age 15, and more than 15% of cases under age 20.[8]

Overall, Hodgkin's disease accounts for just slightly more childhood cases than does non-Hodgkin's lymphoma (NHL).[8] Contrary to the age trend seen with leukemia, incidence rates of lymphoma, especially Hodgkin's disease, increase throughout childhood.[9] Incidence rates of Hodgkin's disease have declined slightly between 1975 and 1995.[8] Over this same period, the 5-year survival rate for Hodgkin's disease has risen to 91%.[8, 10]

Incidence rates of NHL are higher than rates of Hodgkin's disease among children younger than age 10.[8] Over the past 20 years, NHL incidence rates have remained fairly level, except for slight increases among young persons aged 15 to 19. Five-year survival of NHL, although lower than for Hodgkin's disease, has increased substantially, from 43% in the mid-1970s to 73% among those diagnosed between 1989 and 1995.[3]

Central Nervous System and Miscellaneous Intracranial and Intraspinal Neoplasms: Central nervous system (CNS) tumors and associated neoplasms are the second largest category of neoplasms in children, and the most common category of solid tumors, constituting about 20% of all childhood malignancies under age 15.[11] More than half of all CNS malignancies in children and adolescents are astrocytomas.[11] The highest incidence rates of CNS tumors occur among infants and children

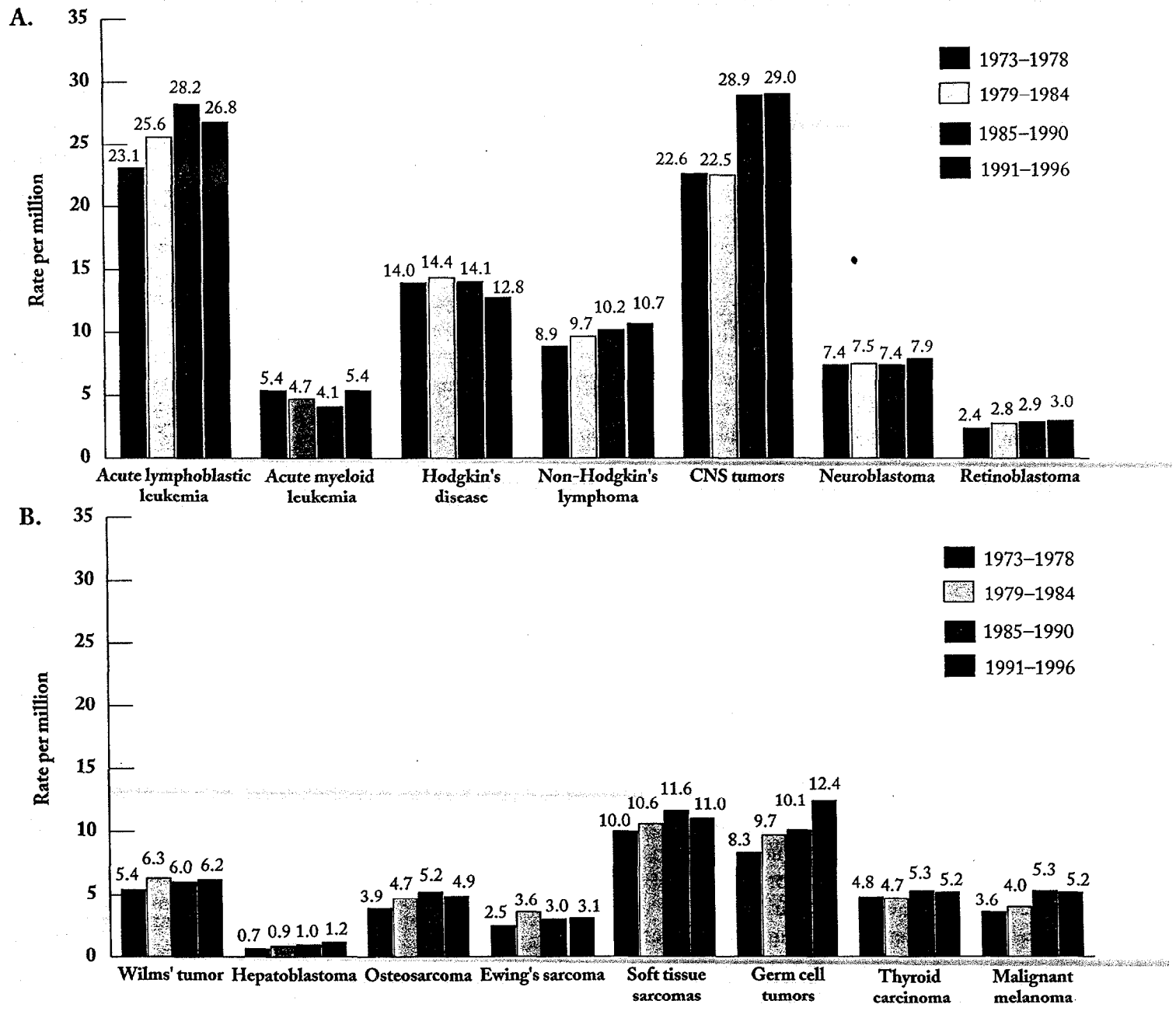
Figure 2. Childhood Cancer (Age 0–19), Age-Adjusted Incidence and Death Rates, 1975–1996



Source: *Pediatric Monograph* 1999, Surveillance, Epidemiology, and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

Figure 3. Age-Adjusted Incidence Rates, Childhood Cancer (Age 0–19), By Period of Diagnosis, 1973–1996



Source: Surveillance, Epidemiology, and End Results Program 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

through age seven. Survival for children with CNS tumors is poorest among infants but improves with increasing age. Five-year survival rates have improved over time to 65%.

Sympathetic and Allied Nervous System Tumors: Cancers in this category are the most common cancers diagnosed in the first year of life. Incidence rates of neuroblastoma, which accounts for more than 97% of cancers in this category, are highest in the first month of life, and decline dramatically with age.[9, 12] Neuroblastoma accounts for 14% of all cancers in children younger than 5 years of age.[13] In contrast with CNS malignancies, survival is highest among infants, and declines with increasing age. Overall, 5-year survival has improved to 64%.[12]

Retinoblastoma: A rare tumor involving the retina, or sometimes the pineal gland, retinoblastoma occurs predominantly in the first few years of life, with 80% of cases diagnosed before age 3.[13] Retinoblastoma accounts for just 2% of cancers under age 20, but 11% of cancers diagnosed in the first year of life, with no differences in incidence by race or gender.[14] Incidence rates and the

favorable 5-year survival, about 94%, remained largely unchanged between 1975 and 1995.[14]

Renal Tumors: Wilms' tumors account for more than 90% of malignancies of the kidney among children and adolescents.[15] Wilms' tumor predominantly occurs in the first five years of life, with incidence rates slightly higher among blacks and females.[13, 14] Incidence rates have not changed substantially between 1975 and 1995, but the 5-year survival rate has improved from 81% to 92% during this period.[15] Survival with Wilms' tumor is slightly higher among females, and for blacks compared with whites.[15]

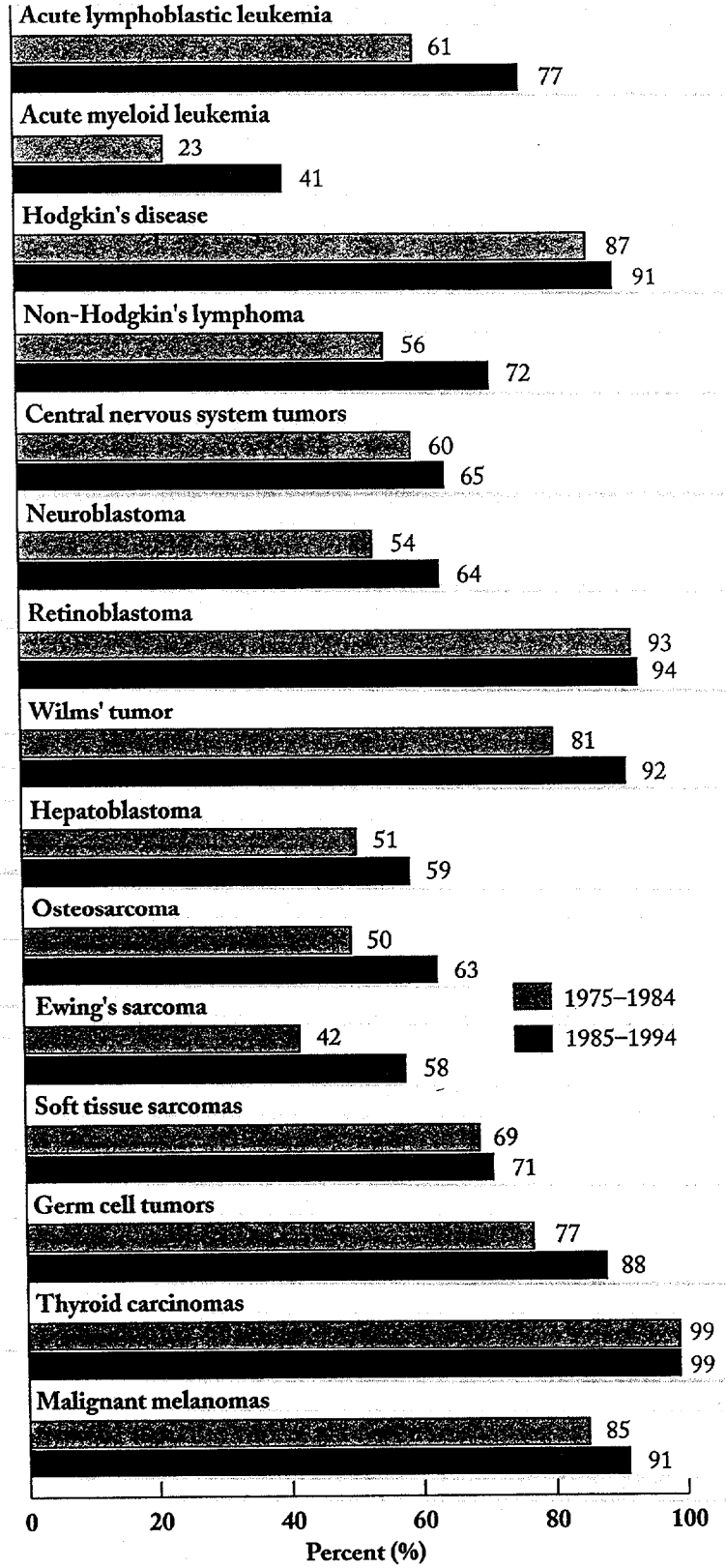
Hepatic Tumors: A rare malignancy in childhood, liver tumors account for just over 1% of childhood cancers.[16] More than two-thirds of hepatic tumors in children are hepatoblastomas.[16] Most cases appear during the first 18 months of life.[17] The remaining percentage of hepatic tumors mostly consist of hepatocellular carcinoma, which does not usually occur before age 15.[16] Five-year survival rates are higher for hepatoblastoma (59%) than for hepatocellular carcinoma (42%), although both have increased over the past 20 years.[16]

Malignant Bone Tumors: Malignant bone tumors constitute 5% to 6% of all childhood cancers. Peak incidence is at age 15, a trend which coincides with adolescent growth spurts.[18] Incidence rates are similar in males and females until after age 13, when male cases become more common[13] Osteosarcoma constitutes 56% of cancers in this category, followed by Ewing's sarcoma, accounting for 34%.[18] Incidence rates of osteosarcoma are slightly higher in blacks than whites, but Ewing's sarcoma is almost 6 times more common in whites than blacks.[18] Five-year survival rates have improved substantially over time, and remain higher for osteosarcoma (63%) than for Ewing's sarcoma (58%).

Soft tissue Sarcomas: Soft tissue sarcomas account for about 7% of cancers diagnosed before age 20. Rhabdomyosarcoma is the most common soft tissue tumor overall, accounting for 50% of cases among children under age 15, although other types of sarcomas account for more than three-fourths of cases diagnosed between ages 15 and 19.[19] Five-year survival rates have not changed much in the past two decades. However, there is a survival advantage for younger patients, males, whites compared with blacks, and if the histologic tissue pattern is embryonal rather than alveolar.[19]

Germ Cell, Trophoblastic and Other Gonadal Neoplasms: This category accounts for just 3.5% of malignancies diagnosed under age 15, but 7% of cancers diagnosed under age 20.[20] Incidence rates increased between 1975 and 1995 among both males and females.[20] Survival rates have improved over this same period, and are higher for

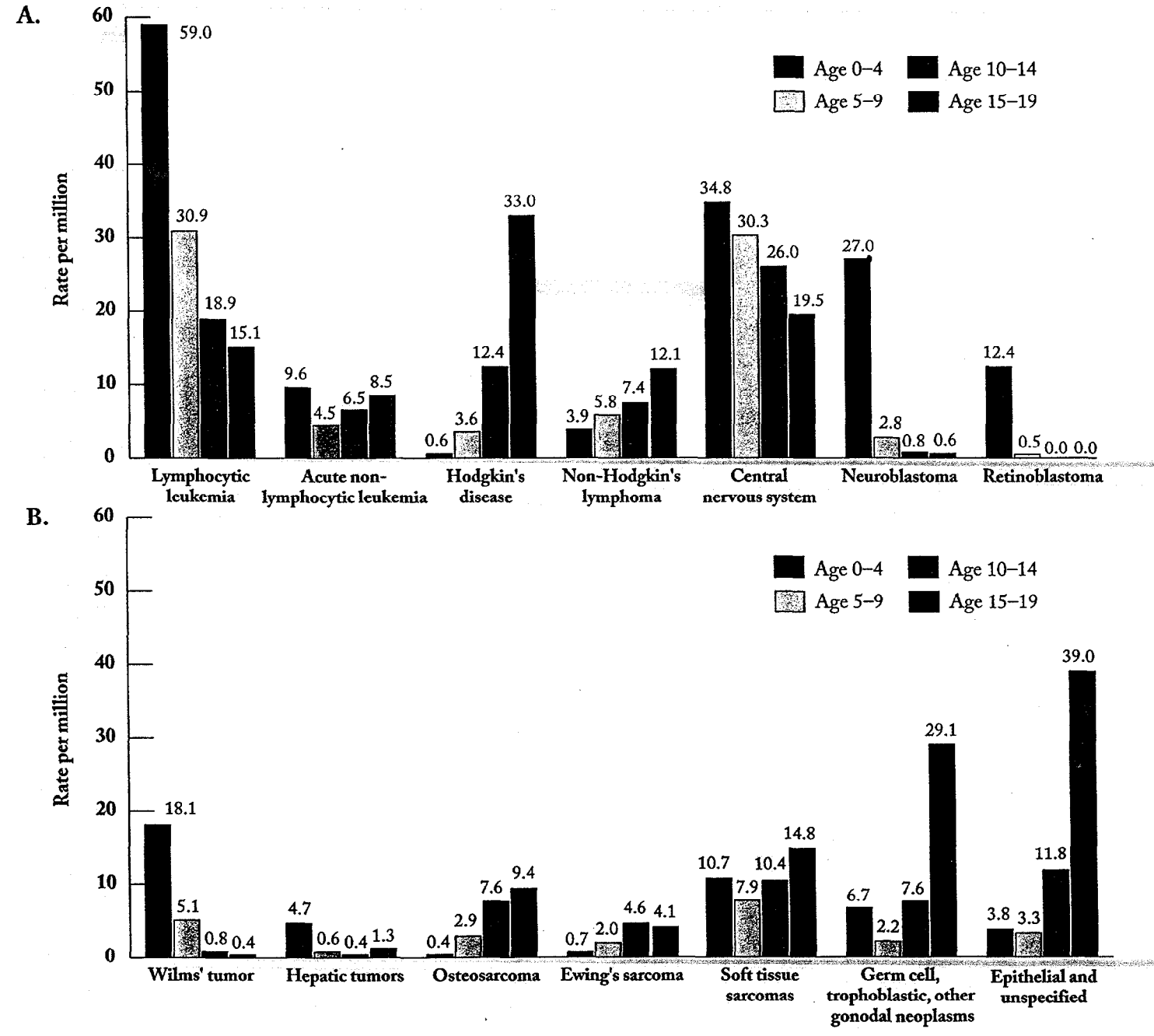
Figure 4. Five-Year Relative Survival, Childhood Cancer (Age 0–19), 1975–1994, By Period of Diagnosis



Source: *Pediatric Monograph* 1999, Surveillance, Epidemiology, and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

Figure 5. Childhood Cancer Incidence Rates, by Age, 1991–1995



Source: Cancer in North America, 1991-1995, North American Association of Central Cancer Registries. American Cancer Society, Surveillance Research

adolescents compared to younger children, for females compared to males, and for whites compared to blacks.[20]

Carcinomas and Other Malignant Epithelial Neoplasms: Carcinomas are rare in individuals younger than 15 years of age. Two-thirds of the carcinomas diagnosed before age 20 are thyroid and melanoma.[21] From ages 15 to 19, thyroid carcinoma is about 5 times more common, and melanoma is about 1.6 times more common among females than males.[21] Five-year survival is high for thyroid carcinoma, 99%, and melanoma, 91%, and is slightly higher among females than males.

Other and Unspecified Malignant Neoplasms: Less than 1% of childhood cancers fall into this category.[2]

Risk Factors for Childhood Cancer

Although it is known that genetic factors and certain prenatal and postnatal exposures can increase the risk of developing some childhood cancers, many of the causes of childhood cancers remain unknown.

Genetic Factors: Children with certain infrequently occurring chromosomal disorders and clinical syndromes are at a greater risk of developing cancer.[13] Strong evidence exists of increased cancer risk among children

with ataxia-telangiectasia, Fanconi's anemia, Bloom syndrome, Li-Fraumeni syndrome, neurofibromatosis, and Down syndrome.[9]

Specific childhood cancers that are unrelated to other hereditary clinical syndromes, but are associated with inherited genetic mutations, include retinoblastoma, Wilms' tumor, and neuroblastoma.[9] Rarely, will cancer occur among more than one child within the same family. If it does, it is likely the result of an inherited susceptibility, common exposure to carcinogens, or a combination of factors.[13]

Prenatal Exposures: Prenatal diagnostic irradiation has been associated with a modest increase in the risk of childhood leukemia.[9] Exposure to ionizing radiation, however, appears to explain only a small proportion of overall cancer incidence in children.[22]

Other in utero exposures have been associated with increased risk of cancer in children. In the early 1970s, an association was discovered between diethylstilbestrol (DES) use by pregnant women and increased risk of clear-cell adenocarcinoma of the vagina in their daughters; half of the cases occurred before age 20.[9] In very rare instances, certain maternal cancers have been transmitted across the placenta to the fetus, including melanoma, lymphoma, and bronchogenic carcinoma.[9]

Postnatal Exposures: Postnatal exposures to ionizing radiation can also increase cancer risk in children. Children who survived atomic warfare had a higher risk of developing both leukemias and solid tumors, as soon as 3 years after exposure.[13] Children who received therapeutic irradiation for benign conditions, such as thymic enlargement or ringworm of the scalp, primarily in the 1940s and 1950s, had a substantially increased risk of developing leukemia, as well as solid tumors of the head and neck, as older children or young adults.[9]

Also, chemotherapy and radiation for childhood cancer increase risk of subsequent cancers. Among survivors of childhood cancer, the risk of a subsequent cancer within 20 years after the first cancer, due to radiation therapy, chemotherapy, or the prior history of cancer itself, has been estimated to be 8% to 9%.[23] However, studies suggest that second childhood cancers (under age 15) are quite uncommon among childhood cancer survivors.[24]

A few cancers of childhood have been associated with specific viral pathogens, most notably nasopharyngeal carcinoma and certain lymphomas associated with Epstein-Barr virus.[13]

Factors under Investigation: A number of additional factors have been studied, but because of inconclusive or inconsistent findings, are not considered to be known risk factors for childhood cancer. For example, some, but not all, studies of prenatal irradiation have shown associations with childhood cancers other than leukemia, including CNS malignancies, osteosarcoma, retinoblastoma, Wilms' tumor, neuroblastomas, and lymphomas.[9] A number of other in utero exposures, including anti-nausea medications, barbiturates, antibiotics, marijuana, frequent alcohol use, and nitrosamine-containing substances, have been implicated in some, but not all, studies of subsequent risk of certain childhood cancers.[9]

A few studies have identified potential associations between some environmental factors, such as pesticides, electromagnetic fields, or motor vehicle exhaust, and certain childhood cancers.[7, 9, 11] However, other studies have not found these associations, and all such studies have been limited in their ability to adequately evaluate and quantify the exposures of interest.[9]

More research is needed to clarify the association, if any, that these factors may have with childhood cancer risk. If any of these factors is truly associated with cancer risk, the magnitude of the effect is expected to be small.

Diagnosis of Childhood Cancer

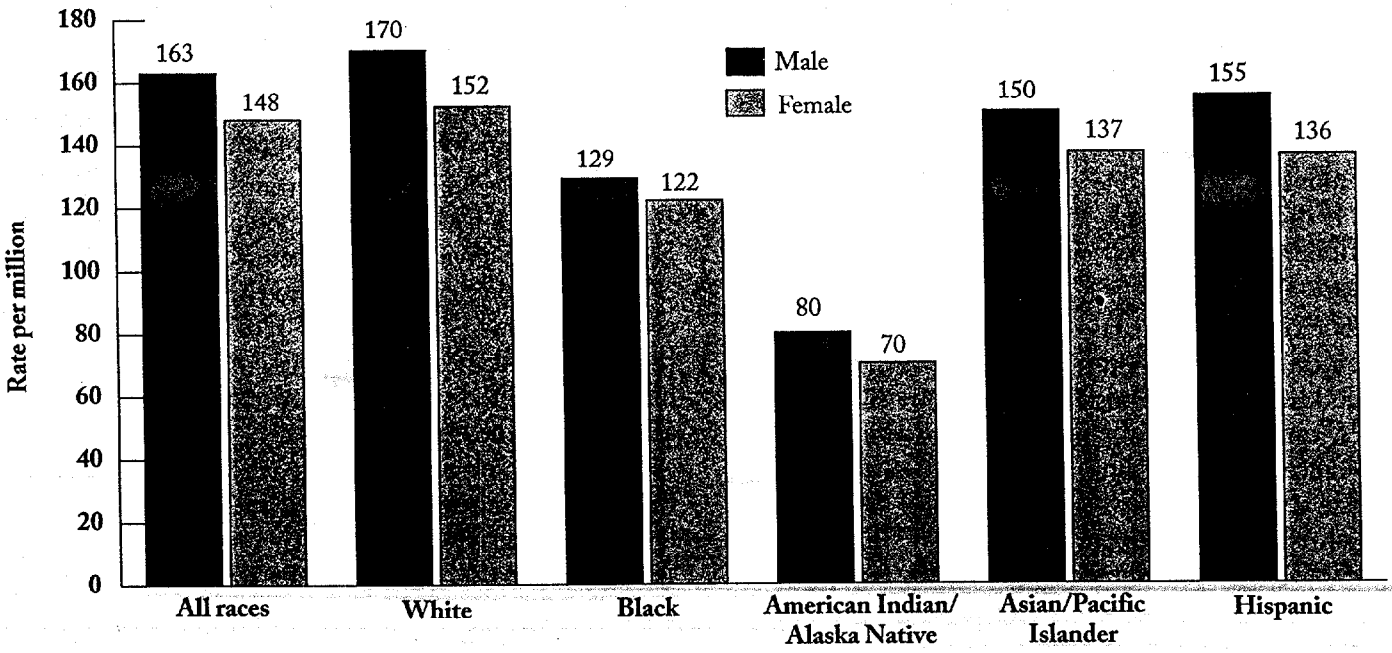
Diagnosis of childhood cancer is sometimes delayed due to the non-specific nature of signs and symptoms, which will vary by cancer type, primary site, and extent of disease.[13] Solid tumors are often first noticed by parents, observing a growing mass, prolonged fever or unexplained pain, in conjunction with weight loss.[13] Children with leukemia may have symptoms such as fever, pallor, bone or joint pain, fatigue, anorexia, cutaneous or mucosal bleeding, or may have no symptoms at all.[25] Children with lymphomas may have no symptoms, or may have swollen lymph nodes, fever, chills, or night sweats.[10]

Treatment of Childhood Cancer

Treatment advances have resulted in substantial improvements in cancer survival and reductions in cancer mortality among children.[9] Children with cancer are treated by chemotherapy, surgery, radiation therapy, or by a combination of two or more of these therapies. Although there are exceptions, childhood cancers tend to respond well to chemotherapy because they grow fast. Most forms of chemotherapy specifically affect growing cells.

For childhood cancers such as osteosarcoma, soft tissue sarcomas, Wilms' tumor, and germ cell tumors, complete surgical excision of the tumor, combined with chemotherapy is the standard approach.[13] Radiation, on the other hand, can cure retinoblastomas, and is used together with surgery or chemotherapy for Wilms' tumor, rhabdomyosarcoma, and Ewing's sarcoma.[13] For acute lymphoblastic leukemia, combination chemotherapy is the primary treatment; however, there is no single

Figure 6. Childhood Cancer (Age 0–19) Age-Adjusted Incidence Rates by Race/Ethnicity and Gender, 1992–1996



Source: SEER Stat Software, Surveillance, Epidemiology, and End Results Program 1973–1996, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

standard regimen, as proper treatment is based on the patient's prognosis which is determined by cytogenetic, immunologic, and molecular laboratory information.[26] Chemotherapy is the main treatment for Hodgkin's disease and non-Hodgkin's lymphoma, with surgery or radiation used for special circumstances.

Children with cancer and their families have special needs that can be best met by children's cancer centers. Treatment in specialized children's cancer centers takes advantage of a team of specialists who understand the differences between adult and childhood cancers, and the unique needs of children with cancer. This team usually includes pediatric oncologists, surgeons, radiation oncologists, pediatric oncology nurses, and nurse practitioners. Many professionals other than doctors and nurses are also involved. Children's cancer centers have psychologists, social workers, child life specialists, nutritionists, rehabilitation and physical therapists, and educators who can support and educate the entire family.

Supportive care is essential to the success and continuation of therapy. By controlling chemotherapy-induced nausea and vomiting, and giving proper nutrition, adequate pain control, and prophylaxis against infection, the complications of treatment can be reduced and the quality of life for childhood cancer patients can be restored. In addition, maintenance of a normal social setting and schooling will relieve some of the stress associated with the alterations and limitations imposed by the treatment.[13]

Current and Future Challenges

Great strides have been made in the treatment of children with cancer, resulting in vastly improved survival and reduced mortality. As survival rates have improved during the past decades, the significance of delayed effects of treatment has become apparent. These effects include the risk of second cancers as well as problems with organ function, growth, and development. One important challenge of pediatric oncology is to continue progress in effectively destroying the cancer, while also minimizing the impact of treatments on the child's long-term quality of life.

Prevention of cancer in children remains a very difficult issue to address. Etiologic studies of childhood cancer are often constrained by methodologic limitations, such as small numbers of cases and difficulty in the assessment of exposure to potentially carcinogenic factors. Other than routine checkups by a pediatrician or other primary care provider, screening programs for early detection of childhood cancer would not be effective because of the rarity of the disease, and the limited ability to identify high risk populations.

Therefore, another challenge is to overcome methodologic limitations in studying the causes of cancer, through multicenter patient enrollment, and improved collection and classification of data on family history and environmental exposures.[9, 23] Additional efforts will be made to evaluate the influence of environmental factors

in the formation of childhood cancers. Finally, greater understanding of the influence of genetics, and of the interaction between genetic predisposition and environmental exposures, will help identify populations at increased risk for childhood cancer, and provide strategies for such children and their families to reduce cancer risk and improve early detection.[9, 27] Improved understanding of genetic causes will also lead to more effective treatments and a marked decrease in their side effects and complications.

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Cancer Around the World, 1994-1997, Death Rates* per 100,000 Population for 45 Countries

Country	All Sites		Oral		Colon & Rectum		Breast	Prostate	Lung & Bronchus		Uterus		Stomach		Leukemia	
	Male	Female	Male	Female	Male	Female	Female	Male	Male	Female	Cervix	Other	Male	Female	Male	Female
United States†	156.0 (24)	108.3 (7)	3.2 (29)	1.1 (23)	15.2 (27)	10.4 (23)	20.0 (14)	15.9 (20)	52.3 (13)	26.6 (2)	2.4 (34)	2.5 (33)	4.4 (44)	2.0 (44)	6.3 (5)	3.7 (10)
Australia‡	156.7 (22)	98.2 (25)	4.1 (26)	1.2 (12)	20.2 (10)	13.3 (10)	19.9 (15)	19.0 (9)	38.8 (29)	13.6 (10)	2.6 (31)	1.7 (43)	6.6 (40)	2.7 (43)	6.1 (6)	3.6 (11)
Austria†	161.0 (21)	99.9 (22)	6.0 (18)	1.1 (27)	21.7 (8)	12.2 (14)	20.9 (13)	16.9 (14)	40.7 (26)	10.3 (16)	2.6 (33)	4.0 (20)	12.8 (24)	6.9 (24)	4.8 (24)	3.2 (18)
Azerbaijan§	117.0 (40)	62.8 (45)	2.3 (38)	0.4 (45)	6.0 (41)	4.2 (43)	8.6 (42)	5.1 (41)	22.3 (38)	3.7 (45)	1.8 (39)	3.7 (23)	24.9 (10)	9.5 (15)	3.9 (38)	2.7 (38)
Bulgaria^	150.0 (28)	86.5 (32)	4.9 (21)	0.8 (39)	17.2 (20)	11.4 (19)	15.9 (31)	8.5 (34)	43.7 (23)	6.6 (32)	4.9 (18)	5.7 (5)	18.5 (19)	8.8 (17)	4.9 (23)	3.0 (33)
Canada‡	156.2 (23)	106.6 (13)	3.8 (27)	1.2 (17)	16.1 (26)	10.3 (25)	21.5 (10)	16.4 (17)	50.0 (14)	23.0 (3)	1.9 (35)	2.2 (38)	6.2 (42)	3.0 (41)	5.5 (17)	3.2 (22)
Chile^	142.5 (32)	105.3 (14)	2.1 (42)	0.6 (43)	7.0 (38)	6.7 (36)	12.1 (35)	16.0 (19)	20.5 (39)	6.4 (33)	10.6 (3)	2.8 (31)	32.2 (3)	11.7 (8)	4.2 (34)	2.7 (39)
China¶^	149.9 (29)	83.5 (37)	2.6 (36)	1.1 (24)	7.9 (36)	6.4 (37)	5.0 (44)	—	37.3 (30)	15.8 (8)	3.0 (27)	—	26.9 (6)	12.7 (4)	3.7 (40)	3.0 (31)
Colombia^	97.7 (43)	89.1 (29)	2.1 (41)	1.2 (19)	4.8 (44)	5.1 (40)	9.1 (40)	12.6 (28)	14.3 (44)	6.8 (30)	9.9 (5)	4.5 (16)	21.4 (13)	13.1 (3)	4.3 (33)	3.7 (9)
Croatia#	212.0 (6)	98.7 (24)	11.4 (4)	1.0 (29)	22.5 (6)	11.5 (18)	18.5 (20)	13.0 (25)	65.1 (6)	8.9 (20)	2.9 (29)	4.9 (9)	20.9 (14)	8.5 (19)	5.7 (12)	3.1 (25)
Cuba‡	127.2 (35)	91.8 (27)	5.5 (20)	1.5 (4)	9.4 (34)	11.3 (20)	14.9 (33)	20.8 (4)	35.7 (31)	12.6 (12)	5.3 (15)	8.3 (1)	6.4 (41)	3.2 (38)	4.6 (28)	3.3 (17)
Czech Republic§	229.3 (3)	124.7 (3)	7.0 (13)	1.2 (16)	34.3 (1)	17.3 (3)	21.1 (12)	16.0 (18)	67.9 (4)	11.4 (14)	5.0 (17)	5.2 (8)	15.5 (23)	7.3 (22)	7.0 (2)	4.2 (6
Denmark§	178.6 (14)	140.0 (1)	4.5 (23)	1.6 (3)	22.7 (5)	15.6 (4)	27.6 (1)	19.9 (6)	49.1 (16)	28.0 (1)	3.8 (21)	3.5 (24)	6.6 (38)	3.1 (40)	6.0 (10)	3.9 (7)
Estonia§	206.2 (8)	102.8 (20)	9.5 (7)	1.3 (7)	18.1 (16)	12.2 (13)	18.5 (19)	12.8 (27)	66.4 (5)	7.0 (28)	5.7 (13)	4.6 (14)	26.0 (8)	12.0 (6)	6.8 (3)	4.9 (1)
Finland‡	142.3 (33)	85.0 (34)	2.2 (39)	1.0 (33)	12.1 (31)	8.5 (31)	16.8 (25)	17.6 (12)	41.2 (25)	6.9 (29)	1.0 (43)	2.4 (34)	10.2 (30)	4.7 (32)	4.7 (25)	3.2 (21)
France‡	188.2 (12)	84.8 (35)	11.3 (5)	1.3 (9)	16.6 (22)	9.6 (29)	19.6 (16)	15.8 (21)	46.5 (19)	6.1 (34)	1.6 (42)	3.4 (26)	7.2 (37)	2.8 (42)	5.6 (14)	3.3 (16)
Germany†	169.5 (17)	103.3 (17)	6.5 (15)	1.2 (14)	20.8 (9)	14.0 (7)	21.7 (8)	16.6 (16)	45.4 (20)	9.4 (17)	2.8 (30)	2.8 (30)	12.0 (26)	6.3 (27)	5.5 (16)	3.5 (14)
Greece§	145.7 (31)	78.2 (41)	1.9 (44)	0.6 (44)	8.0 (35)	6.2 (38)	16.2 (27)	9.3 (33)	49.8 (15)	7.1 (25)	0.9 (44)	2.3 (35)	8.2 (36)	4.3 (34)	6.0 (9)	3.6 (12)
Hungary^^	272.2 (1)	138.4 (2)	20.0 (1)	2.4 (1)	34.3 (2)	18.7 (2)	23.7 (6)	18.7 (11)	85.6 (1)	20.3 (5)	6.5 (10)	4.8 (13)	18.8 (18)	8.7 (18)	7.4 (1)	4.4 (4)
Ireland‡	171.6 (16)	121.0 (5)	4.4 (24)	1.3 (8)	22.5 (7)	13.3 (9)	26.1 (2)	18.8 (10)	44.5 (22)	18.6 (7)	3.1 (26)	2.3 (36)	10.7 (28)	5.1 (30)	4.6 (27)	3.0 (34)
Israel§	127.1 (36)	104.5 (15)	1.5 (45)	0.7 (40)	17.9 (18)	13.8 (8)	25.1 (4)	12.0 (30)	27.1 (35)	8.7 (21)	1.7 (41)	3.0 (27)	8.6 (34)	5.1 (31)	6.1 (8)	4.2 (5)
Japan**	155.2 (25)	75.7 (42)	3.1 (31)	0.8 (37)	17.1 (21)	9.9 (28)	7.7 (43)	5.1 (42)	31.7 (33)	8.5 (22)	1.9 (36)	2.0 (42)	30.2 (4)	12.3 (5)	4.1 (36)	2.5 (41)
Kazakhstan§	207.6 (7)	102.9 (19)	7.7 (11)	1.9 (2)	12.6 (30)	8.6 (30)	13.2 (34)	5.7 (39)	62.3 (10)	8.5 (23)	6.2 (12)	4.6 (15)	33.1 (2)	13.9 (2)	3.3 (43)	2.6 (40)
Kyrgyzstan§	123.5 (37)	72.4 (43)	3.6 (28)	1.0 (31)	6.9 (39)	4.5 (41)	10.6 (37)	4.3 (43)	25.5 (36)	4.3 (40)	6.2 (11)	3.5 (25)	29.1 (5)	10.7 (10)	2.5 (45)	2.0 (45)
Latvia‡	224.0 (4)	107.6 (9)	7.9 (10)	1.2 (21)	18.3 (12)	11.8 (15)	17.3 (24)	11.5 (31)	63.6 (8)	5.9 (37)	4.2 (19)	5.4 (7)	26.8 (7)	11.8 (7)	5.8 (11)	3.8 (8)
Lithuania§	203.7 (10)	101.0 (21)	8.5 (9)	1.0 (30)	18.2 (13)	11.7 (16)	18.7 (18)	15.2 (22)	62.5 (9)	5.3 (38)	7.4 (7)	4.8 (12)	25.9 (9)	10.2 (11)	6.6 (4)	4.5 (3)
Macedonia§	137.4 (34)	82.3 (38)	2.6 (35)	0.7 (42)	10.8 (33)	7.1 (34)	16.1 (30)	6.2 (38)	39.6 (28)	6.7 (31)	3.1 (25)	5.5 (6)	22.0 (11)	9.7 (13)	4.4 (31)	2.4 (42)
Mauritius§	80.3 (45)	65.2 (44)	4.3 (25)	1.2 (20)	6.0 (42)	3.8 (44)	9.0 (41)	7.7 (36)	16.7 (42)	4.0 (41)	5.5 (14)	8.3 (2)	10.8 (27)	5.7 (28)	3.5 (41)	2.1 (44)
Mexico‡	85.0 (44)	78.9 (40)	1.9 (43)	0.7 (41)	3.6 (45)	3.3 (45)	9.3 (39)	12.8 (26)	16.2 (43)	6.0 (35)	14.0 (1)	2.1 (41)	9.7 (31)	7.1 (23)	3.9 (39)	3.1 (28)
Netherlands‡	182.3 (13)	108.0 (8)	2.8 (33)	1.0 (32)	17.7 (19)	12.7 (11)	26.0 (3)	19.4 (8)	62.0 (11)	13.6 (9)	1.7 (40)	2.2 (37)	10.3 (29)	4.2 (35)	5.7 (13)	3.1 (29)
New Zealand^	167.2 (18)	121.2 (4)	2.7 (34)	1.2 (13)	26.4 (3)	19.1 (1)	22.9 (7)	19.8 (7)	39.6 (27)	18.8 (6)	3.4 (23)	2.1 (40)	6.0 (43)	3.2 (39)	6.1 (7)	4.5 (2
Norway‡	146.6 (30)	103.3 (18)	3.1 (30)	1.0 (34)	20.0 (11)	14.7 (5)	19.4 (17)	23.2 (2)	31.7 (32)	13.3 (11)	3.1 (24)	2.9 (29)	9.1 (33)	4.6 (33)	4.3 (32)	2.8 (3
Poland§	204.9 (9)	107.6 (11)	6.3 (17)	1.1 (25)	16.4 (23)	11.0 (22)	16.1 (29)	11.1 (32)	71.3 (2)	11.1 (15)	7.3 (8)	3.8 (22)	18.9 (17)	6.8 (25)	5.6 (15)	3.5 (15)
Portugal§	155.0 (26)	84.3 (36)	6.4 (16)	0.8 (38)	18.1 (15)	10.4 (24)	17.6 (22)	17.2 (13)	29.2 (34)	4.6 (39)	2.6 (32)	4.1 (18)	21.8 (12)	10.0 (12)	5.0 (22)	3.2 (19)
Rep. of Moldova‡	162.4 (20)	88.9 (30)	11.7 (3)	1.3 (10)	16.2 (25)	11.1 (21)	18.2 (21)	5.7 (40)	43.0 (24)	6.0 (36)	6.6 (9)	4.4 (17)	20.7 (15)	9.2 (16)	5.2 (20)	3.1 (26)
Romania§	150.7 (27)	88.5 (31)	7.1 (12)	1.2 (18)	11.3 (32)	7.9 (33)	15.7 (32)	8.3 (35)	44.8 (21)	7.2 (24)	10.5 (4)	4.1 (19)	17.6 (21)	6.8 (26)	4.5 (29)	3.0 (30)
Russian Fed.‡	237.1 (2)	107.6 (10)	9.1 (8)	1.1 (26)	18.2 (14)	12.6 (12)	16.1 (28)	7.2 (37)	70.5 (3)	7.0 (27)	5.0 (16)	4.9 (11)	36.9 (1)	15.3 (1)	5.1 (21)	3.5 (13)
Slovakia‡	218.1 (5)	103.5 (16)	16.8 (2)	1.2 (15)	14.6 (28)	6.8 (35)	—	12.2 (29)	64.2 (7)	7.1 (26)	—	1.0 (44)	—	—	3.4 (42)	2.2 (43)
Slovenia§	200.9 (11)	107.4 (12)	10.7 (6)	1.0 (28)	23.9 (4)	14.0 (6)	21.2 (11)	14.7 (23)	61.1 (12)	9.1 (19)	4.0 (20)	4.9 (10)	19.7 (16)	8.3 (20)	5.4 (18)	3.2 (20)
Spain‡	173.2 (15)	79.8 (39)	7.0 (14)	0.9 (36)	16.4 (24)	10.0 (27)	17.5 (23)	13.9 (24)	48.7 (17)	3.9 (42)	1.8 (38)	3.0 (28)	12.7 (25)	5.6 (29)	5.2 (19)	3.2 (23)
Sweden§	123.3 (38)	94.4 (26)	2.2 (40)	0.9 (35)	13.8 (29)	10.2 (26)	16.8 (26)	21.4 (3)	22.3 (37)	12.0 (13)	1.8 (37)	2.5 (32)	6.6 (39)	3.5 (37)	4.5 (30)	3.2 (24)
Trinidad & Tobago^	107.3 (41)	99.4 (23)	4.6 (22)	1.4 (6)	7.8 (37)	8.3 (32)	21.5 (9)	35.5 (1)	11.2 (45)	3.7 (44)	8.2 (6)	7.1 (4)	8.4 (35)	7.7 (21)	4.2 (35)	2.9 (36)
Turkmenistan^	120.8 (39)	86.0 (33)	5.8 (19)	1.5 (5)	6.2 (40)	4.4 (42)	9.5 (38)	1.4 (44)	17.3 (41)	3.7 (43)	3.7 (22)	3.8 (21)	18.3 (20)	11.0 (9)	3.1 (44)	2.9 (35)
United Kingdom†	164.2 (19)	116.5 (6)	2.9 (32)	1.1 (22)	18.0 (17)	11.6 (17)	24.5 (5)	16.6 (15)	46.6 (18)	20.5 (4)	3.0 (28)	2.1 (39)	9.5 (32)	3.9 (36)	4.7 (26)	3.0 (32)
Venezuela^	104.3 (42)	90.0 (28)	2.5 (37)	1.2 (11)	5.9 (43)	6.2 (39)	11.8 (36)	20.3 (5)	19.4 (40)	9.3 (18)	10.8 (2)	7.4 (3)	16.8 (22)	9.7 (14)	4.1 (37)	3.1 (27)

Note: Figures in parentheses are order of rank within site and sex group. *Rates are age-adjusted to the World Health Organization world standard population.

†94-97 ‡94-95 §94-96 ^94 only ¶Oral cancer mortality rate includes nasopharynx only #95-96 ^^96-97 **95-97

Source: Mortality Database 1994–1997, World Health Organization, 1999.

American Cancer Society, Surveillance Research

CANCER IN MINORITIES

In 2000, about 1,220,100 cancers are expected to be diagnosed in the United States and 552,200 Americans are expected to die of this disease.

Overall, blacks are more likely to develop cancer than persons of any other racial and ethnic group. During 1990-1996, incidence rates were 442.9 per 100,000 among blacks, 402.9 per 100,000 among whites, 275.4 per 100,000 among Hispanics, 279.1 per 100,000 among Asian/Pacific Islanders, and 153.4 per 100,000 among American Indians. During these same years, cancer incidence rates decreased among whites (-1.2% per year), Hispanics (-1.7% per year), and American Indians (-0.7% per year), and remained relatively stable among blacks and Asian/Pacific Islanders.

The incidence rate of female breast cancer is highest among white women (113.2 per 100,000) and lowest among American Indian women (33.9 per 100,000). black women have the highest incidence rates of colon and rectum (44.9 per 100,000) and lung and bronchus cancer (46.2 per 100,000) followed by whites, Asian/Pacific Islanders, Hispanics, and American Indians.

Black men have the highest incidence rates of prostate (222.9 per 100,000), colon and rectum (58.1 per 100,000), and lung and bronchus cancer (112.3 per 100,000). Black men are at least 50% more likely to develop prostate cancer than men of any other racial and ethnic group. Similar to rates in American Indian women, American Indian men have consistently lower

Incidence and Mortality Rates* by Site, Race, and Ethnicity, United States, 1990-1996

Incidence	White	Black	Asian/Pacific Islander	American Indian	Hispanic†
All Sites					
Males	480.2	598.0	325.5	177.8	326.9
Females	351.6	335.6	244.9	136.8	243.2
Total	402.9	442.9	279.1	153.4	275.4
Breast (female)	113.2	99.3	72.6	33.9	69.4
Colon & rectum					
Males	53.2	58.1	47.5	21.5	35.7
Females	36.8	44.9	31.4	12.4	24.0
Total	43.9	50.4	38.6	16.4	29.0
Lung & bronchus					
Males	73.1	112.3	52.4	25.3	38.8
Females	43.3	46.2	22.5	13.5	19.6
Total	55.9	73.9	35.8	18.6	27.6
Prostate	147.3	222.9	81.5	46.5	102.8

Mortality	White	Black	Asian/Pacific Islander	American Indian	Hispanic†
All Sites					
Males	208.8	308.8	129.2	123.3	131.8
Females	139.8	168.1	83.5	90.2	86.3
Total	167.5	223.4	103.4	104.0	104.9
Breast (female)	25.7	31.4	11.4	12.3	15.3
Colon & rectum					
Males	21.5	27.8	13.4	11.0	13.2
Females	14.5	20.0	9.0	8.9	8.4
Total	17.4	23.1	10.9	9.9	10.4
Lung & bronchus					
Males	70.1	100.8	34.9	40.5	32.0
Females	33.8	32.8	14.9	19.8	11.0
Total	49.3	60.5	23.7	28.8	19.9
Prostate	23.7	54.8	10.7	14.3	16.7

*Per 100,000, age-adjusted to the 1970 US standard population. †Hispanic is not mutually exclusive from being a member of another ethnic group.

Note: Incidence data are from the 11 SEER areas; mortality data, except data for Hispanics, are from all states; data for Hispanics include deaths that occurred in all states except Connecticut, Louisiana, New Hampshire, and Oklahoma.

Source: US Mortality 1973–1996, National Center for Health Statistics, Centers for Disease Control and Prevention 1999, SEER Incidence 1973–1996, Surveillance, Epidemiology, and End Results Program, Division of Cancer Control and Population Sciences, National Cancer Institute.

American Cancer Society, Surveillance Research

rates of cancer incidence than men of other racial and ethnic groups.

Blacks are about 33% more likely to die of cancer than whites, and are 2 times more likely to die of cancer than Asian/Pacific Islanders, American Indians, and Hispanics. During 1990-1996, cancer mortality rates were 223.4 per 100,000 among blacks, 167.5 per 100,000 among whites, 104.9 per 100,000 among Hispanics, 103.4 per 100,000 among Asian/Pacific Islanders, and 104.0 per 100,000 among American Indians. Cancer mortality rates for many racial and ethnic groups have begun to decline recently. During 1990-1996, mortality rates decreased among whites (-0.5% per year), blacks (-0.9% per year), and Hispanics (-0.6% per year); remained relatively stable among Asian/Pacific Islanders; and increased slightly among American Indians (0.9 % per year).

Black women are more likely to die of breast (31.4 per 100,000) and colon and rectum cancer (20.0 per 100,000) than are women of any other racial and ethnic group. White and black women have the highest mortality rates of lung and bronchus cancer followed by American Indian, Asian/Pacific Islander, and Hispanic women.

Black men have the highest mortality rates of colon and rectum (27.8 per 100,000), lung and bronchus (100.8 per 100,000), and prostate cancer (54.8 per 100,000). Black men are more than twice as likely to die of prostate cancer than men of other racial and ethnic groups.

For more information about cancer in minority populations, please inquire about the American Cancer Society publication *Cancer Facts & Figures for African Americans* (8614.98).

Tobacco Use

Smoking is the most preventable cause of death in our society. During 1995, approximately 2.1 million people in developed countries died as a result of smoking.[1] Tobacco use is responsible for nearly one in five deaths in the United States. Based on data from the American Cancer Society's Cancer Prevention Study II, it is estimated that 430,700 US deaths per year were attributable to smoking during 1990-1994.[2] Although the number of cardiovascular deaths is declining, smoking-related cancer deaths continue to rise. Approximately half of all continuing smokers die prematurely from smoking. Of these, approximately half die in middle age (35-69), losing an average of 20 to 25 years of life expectancy.

Lung cancer mortality rates are about 23 times higher for current male smokers and 13 times higher for current female smokers compared to lifelong never-smokers.[3] In addition to being responsible for 87% of lung cancers, smoking is also associated with cancers of the mouth, pharynx, larynx, esophagus, pancreas, uterine cervix, kidney, and bladder. Smoking accounts for at least 30% of all cancer deaths, is a major cause of heart disease, and is associated with conditions ranging from colds and gastric ulcers to chronic bronchitis, emphysema, and cerebrovascular disease.

Trends in Smoking

Cigarette smoking among adults aged 18 and over declined 40% between 1965 and 1990—from 42% to 25%.[4] However, overall smoking prevalence was virtually unchanged between 1990 and 1995.

- Between 1978 and 1995, smoking prevalence among men 18 years and older declined for whites (37% to 28%), blacks (45% to 31%), Hispanics (38% to 23%), and Asian/Pacific Islanders (33% to 25%). Among American Indian/Alaska Native men, smoking prevalence did not change from 1983 to 1995.[5]
- Between 1978 and 1995, smoking prevalence among women 18 years and older declined for whites (31% to 24%), blacks (31% to 23%), Hispanics (23% to 15%), and Asian/Pacific Islanders (15% to 6%). Smoking prevalence among American Indian/Alaska Native women remained unchanged from 1978 to 1995.[5]
- Between 1983 and 1995, smoking prevalence among college graduates decreased by one-third from 21% to 14% and among adults without a high school education decreased only 12% from 41% to 36%.[1]
- Per capita consumption of cigarettes continues to decline. After peaking at 4,345 in 1963, consumption among Americans 18 years and older has decreased 46% to an estimated 2,350 in 1998.[6]
- From 1991 to 1997, the prevalence of current cigarette smoking among high school students increased 32%. Current cigarette smoking increased 80% among black students, 34% among Hispanic students, and 28% among white students.[4]
- Past-month smoking rates among US high school students are on the rise—increasing by nearly a third from 27.5% in 1991 to 36.4% in 1997. Nearly one-half (48.2%) of male students and more than one-third (36.0%) of female students reported using some

form of tobacco—cigarettes, cigars, or smokeless tobacco—in the past month.[4]

Profile of Smokers

The 1997 National Health Interview Survey (NHIS)[7] data show that:

- An estimated 48 million US adults (25.7 million men and 22.3 million women) were current smokers.
- Men are more likely to smoke (27.6%) than women (22.1%).
- Smoking prevalence was highest among American Indian/Alaska Natives (34.1%) compared with other racial and ethnic groups.
- Smoking prevalence was highest among men who had dropped out of high school (41.3%).

The 1997 Youth Risk Behavior Surveillance System (YRBSS) shows that:[8]

- Nationwide, 70.2% of high school students have tried cigarette smoking.
- More than one-third (36.4%) of high school students were current cigarette smokers, i.e., smoked at least one cigarette in the past month.
- Seventeen percent of high school students smoked cigarettes on at least 20 of the 30 days preceding the survey.
- White students (19.9%) were more likely than black students (7.2%) or Hispanic students (10.9%) to smoke frequently.

Cigars

The consumption of large cigars and cigarillos has been increasing since 1993.[6] The production of small cigars rose dramatically to 1,750 million, 18% above the 1997 production.[6] Overall cigar use should exceed 5.3 billion in 1998 and the trend is expected to continue in 1999.[6]

- The rates of cigar smoking increased from 1990 to 1996 among adult males, with the greatest increase in occasional cigar smoking among younger men (aged 18 to 24) and men with at least a college degree.[9]
- In 1997, overall prevalence of smoking at least one cigar in the past 30 days was 22% among high school students; males (31.2%) were more likely to have smoked cigars than females (10.8%).[8]
- US students in Grades 9-12 who used other tobacco products (cigarettes, smokeless tobacco) were more likely to report smoking cigars. Nearly three-fourths of male and one-third of female cigarette smokers reported smoking at least one cigar in the past year.[10] Twenty percent of males and 7.8% of females in Grades 9-12 who were not cigarette smokers have smoked a cigar in the past year.[11]

Congress did not explicitly include cigars in the 1984 law requiring health warnings on cigarettes, so cigar packages have no warning from the US Surgeon General. The following health consequences of cigar smoking are presented in the 1998 National Cancer Institute Monograph:[12]

- Most of the same carcinogens and cancer-producing chemicals found in cigarettes are found in cigars.
- Regular cigar smoking causes cancer of the lung, oral cavity, larynx, esophagus, and probably cancer of the pancreas.
- Similar to cigarette smokers, cigar smokers have 4 to 10 times greater risk of dying from laryngeal, oral, or esophageal cancers compared with nonsmokers.

Smoking Cessation

In September 1990, the US Surgeon General outlined the benefits of smoking cessation:[13]

- People who quit, regardless of age, live longer than people who continue to smoke.
- Smokers who quit before age 50 have half the risk of dying in the next 15 years compared with those who continue to smoke.
- Quitting smoking substantially decreases the risk of lung, laryngeal, esophageal, oral, pancreatic, bladder, and cervical cancers.
- Quitting lowers the risk for other major diseases including coronary heart disease and cardiovascular disease.

The 1997 NHIS[7] shows:

- About 40.7% of current every-day smokers attempted to quit attempts for at least one day during the preceding 12 months.
- About 22.8% of US adults (25.1 million men and 19.2 million women) were former smokers.

Teenagers find it very difficult to quit smoking—72.9% of teens who had ever smoked daily had tried to quit and only 13.5% had been successful.[14] The 1990-1992 National Comorbidity Survey estimated that 23.6% of persons aged 15-24 years who ever used cigarettes went on to become addicted. This conversion rate (from use to dependence) was similar to rates for use of cocaine (24.5%) and heroin (20.1%).[14] Although approximately 70% of adolescent smokers regret ever starting, cessation programs designed for young people have had very low success rates.[15]

Secondhand Smoke

Secondhand smoke, also known as environmental tobacco smoke (ETS) is a human carcinogen for which there is no safe level of exposure. This is the conclusion

reached by numerous scientific bodies that have conducted extensive reviews of current data, including the US Environmental Protection Agency,[16] California Environmental Protection Agency,[17] and the National Institute of Environmental Sciences' National Toxicology Program's Board of Scientific Counselors.[18]

- Each year, about 3,000 nonsmoking adults die of lung cancer as a result of breathing secondhand smoke.
- ETS causes an estimated 35,000 to 40,000 deaths from heart disease in people who are not current smokers.
- Secondhand smoke causes other respiratory problems in nonsmokers: coughing, phlegm, chest discomfort, and reduced lung function.
- Each year, exposure to secondhand smoke causes 150,000 to 300,000 lower respiratory tract infections (such as pneumonia and bronchitis) in US infants and children younger than 18 months of age. These infections result in 7,500 to 15,000 hospitalizations every year.
- Secondhand smoke increases the number of asthma attacks and the severity of asthma in about 20% of this country's 2 to 5 million asthmatic children.
- Four chemicals in secondhand smoke (benzene, 2-naphthylamine, 4-aminobiphenyl, and polonium-210) are known human carcinogens, based on EPA standards. Ten other chemicals in secondhand smoke are classified by the EPA as probable human carcinogens.

Because there are no safe levels of secondhand smoke, it is important that public policies to protect people from secondhand smoke be as strong as possible.

Cigarette Exports

US cigarette exports approximately quadrupled from 1986 to 1996, largely due to aggressive marketing by tobacco companies and expanding foreign markets. According to the US Department of Agriculture:[6]

- Between 1996 and 1998, cigarette exports fell from 243 to 201 billion sticks. This decline is largely due to the fact that US companies have greatly expanded overseas production capacity and reduced their dependence on US exports.
- US export destinations include Japan, which imported a record 70.9 billion cigarettes in 1998; the European Union, which imported 48.9 billion cigarettes; and Russia, Azerbaijan, and the Ukraine, which imported 17.6 billion cigarettes in 1998.

Smokeless Tobacco

In 1986, the US Surgeon General concluded that the use of smokeless tobacco[19] is not a safe substitute for smoking cigarettes. It can cause cancer and a number of non-cancerous oral conditions and can lead to nicotine addiction and dependence.[19]

- Oral cancer occurs several times more frequently among snuff dippers compared with non-tobacco users.
- The excess risk of cancer of the cheek and gum may reach nearly 50-fold among long-term snuff users.
- According to the US Department of Agriculture, US output of moist snuff has risen 50% in the past decade from 41 million pounds in 1988 to an estimated 61 million pounds in 1998.[6, 20]
- The YRBSS reported that about 15.8% of male high school students currently used chewing tobacco or snuff in 1997.[6]
- Among adults aged 18 and older, 5.9% of men and 0.6% of women were current users of chewing tobacco or snuff according to aggregated 1987 and 1991 NHIS data.[5] American Indian/Alaska Native (7.8%) and white (6.8%) men were more likely than black (3.1%), Hispanic (1.5%), and Asian/Pacific Islander men (1.2%) to use smokeless tobacco.

Costs of Tobacco

Tobacco costs to our society are best measured by the number of people who die or suffer illness because of its use. Tobacco use also drains the US economy of more than $100 billion in health care costs and lost productivity.[21] Health care expenditures caused directly by smoking totaled $50 billion in 1993, according to the Centers for Disease Control and Prevention. Forty-three percent of these costs were paid by government funds, including Medicaid and Medicare. Tobacco costs Medicare more than $10 billion per year.[21] Smoking costs Medicaid alone $12.9 billion per year—about one-seventh of the total Medicaid budget. The impact of cigarette smoking on state Medicaid budgets varies among states, ranging from $1.9 billion in New York to $11.4 million in Wyoming.[22] Lost productivity caused by smoking cost the US economy $47.2 billion in 1990, according to the Office of Technology Assessment.[23] Adjusted for inflation, the total economic cost of smoking is more than $100 billion per year. This does not include costs associated with diseases caused by environmental tobacco smoke, burn care resulting from cigarette smoking-related fires, or perinatal care for low-

birthweight infants of mothers who smoke. Even though smokers die younger than the average American, over the course of their lives, current and former smokers generate an estimated $501 billion in excess health care costs.[24] On average, each cigarette pack sold costs Americans more than $3.90 in smoking-related expenses.[25]

For more information about tobacco use, other preventable cancer risk factors, and early detection for cancer, please inquire about the annual American Cancer Society publication *Cancer Prevention & Early Detection Facts & Figures,* formerly known as *Cancer Risk Report* (8600.99).

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NUTRITION AND DIET

Scientific evidence suggests that about one-third of the cancer deaths that occur in the US each year is due to the adult diet, including its effect on obesity. Another third is due to cigarette smoking. Therefore, for the majority of Americans who do not use tobacco, dietary choices and physical activity become the most important modifiable determinants of cancer risk. The evidence also indicates that although inherited genes do influence cancer risk, heredity alone explains only a fraction of all cancer. Behavioral factors such as tobacco use, dietary choices, and physical activity modify the risk of cancer at all stages of its development. The introduction of healthful diet and exercise practices at any time from childhood to old age can promote health and probably reduce cancer risk.

Many dietary factors can affect cancer risk: types of foods, food preparation methods, portion sizes, food variety, and overall caloric balance. Cancer risk can be reduced by an overall dietary pattern that includes a high proportion of plant foods (fruits, vegetables, grains, and beans), limited amounts of meat, dairy, and other high-fat foods, and a balance of caloric intake and physical activity.

Based on its review of the scientific evidence, the American Cancer Society updated its nutrition guidelines in 1999. The Society's recommendations are consistent in principle with the 1992 US Department of Agriculture (USDA) Food Guide Pyramid, the 1995 Dietary Guidelines for Americans, and dietary recommendations of other agencies for general health promotion and for the prevention of coronary heart disease, diabetes, and other diet-related chronic conditions. Although no diet can guarantee full protection against any disease, the Society believes that the following recommendations offer the best nutrition information currently available to help Americans reduce their risk of cancer.

Choose most of the foods you eat from plant sources.

Eat five or more servings of fruits and vegetables each day; eat other foods from plant sources, such as breads, cereals, grain products, rice, pasta, or beans several times each day. Many scientific studies show that eating fruits and vegetables (especially green and dark yellow vegetables and those in the cabbage family, soy products, and legumes) protect against cancers at many sites, particularly for cancers of the gastrointestinal and respiratory tracts. Grains are an important source of many vitamins and minerals such as folate, calcium, and selenium, which have been associated with a lower risk of colon cancer in some studies. Beans (legumes) are especially rich in nutrients that may protect against cancer.

Limit your intake of high-fat foods, particularly from animal sources.

Choose foods low in fat; limit consumption of meats, especially high-fat meats. High-fat diets have been associated with an increase in the risk of cancers of the colon and rectum, prostate, and endometrium. The association between high-fat diets and the risk of breast cancer is much weaker. Whether these associations are caused by the total amount of fat, the particular type of fat (saturated, monounsaturated, or polysaturated), the calories contributed by fat, or some other factor in food fats, has not yet been determined. Consumption of meat, especially red meat, has been associated with increased cancer risk at several sites, most notably colon and prostate.

Be physically active: achieve and maintain a healthy weight.

Physical activity can help protect against some cancers, either by balancing caloric intake with energy expenditure or by other mechanisms. An imbalance of caloric intake and energy output can lead to being overweight or obese, and to increased risk for cancers at several sites: colon and rectum, prostate, endometrium, breast (among postmenopausal women), and kidney. Both physical activity and controlled caloric intake are necessary to achieve or to maintain a healthy body weight.

Limit consumption of alcoholic beverages, if you drink at all.

Alcoholic beverages, along with cigarette smoking and use of snuff and chewing tobacco, cause cancers of the oral cavity, esophagus, and larynx. The combined use of tobacco and alcohol leads to a greatly increased risk of oral and esophageal cancers; the effect of tobacco and alcohol combined is greater than the sum of their individual effects. Studies also have noted an association between alcohol consumption and an increased risk of breast cancer. The mechanism of this effect is not yet known, but the association may be due to carcinogenic actions of alcohol or its metabolites, to alcohol-induced changes in levels of hormones such as estrogens, or to some other process. Regardless of the mechanism, studies show that the risk of breast cancer increases with an intake beginning at just a few drinks per week. Reducing alcohol consumption is a good way for women who drink regularly to reduce their risk of breast cancer.

Environmental Cancer Risks

Environmental factors (including smoking, diet, and infectious diseases) probably account for three quarters of all cancer cases in the United States. For most people, the risks from carcinogens in tobacco smoke and from nutritional factors, including obesity and physical inactivity, have a larger effect on personal cancer risk than do pollutants in food, drinking water, and air. However, for both voluntary and involuntary exposures, the degree of cancer hazard depends on the concentration, intensity, and duration of exposure. Substantial increases in risk have been demonstrated in occupational settings where workers have been exposed to high concentrations of certain chemicals, metals, and other exposures, as well as among radiation victims, and patients treated with drugs or therapies later found to be carcinogenic.

Even low-dose exposures that pose only a small risk to individuals can represent significant public health hazards if the exposures are widespread (for example, secondhand tobacco smoke). Strong regulatory control and continuing attention to safe occupational practices, drug testing, and consumer product safety play an important role in minimizing these risks.

Risk Assessment

Risk assessment is not perfect. For most potential carcinogens, data are only available from high dose experiments in animals or highly exposed occupational groups. To use such information to set human safety standards, regulators must extrapolate from animals to humans and from high-dose to low-dose conditions. Because both extrapolations involve much uncertainty, as does the effect of mixtures of chemicals and of especially susceptible subgroups of the population, risk assessment generally makes conservative assumptions to err on the side of safety. For cancer safety standards, only increased risks of one case or less per million persons over a lifetime are usually acceptable.

Safety standards developed in this way for chemical or radiation exposures are the basis for federal regulatory activities at the Food and Drug Administration, the Environmental Protection Agency, and the Occupational Safety and Health Administration. The application of laws and procedures by which standards are implemented and risks are controlled is called risk management.

Chemicals

Various chemicals (for example, benzene, asbestos, vinyl chloride, arsenic, aflatoxin) show definite evidence of human carcinogenicity; others are considered probable human carcinogens based on evidence from animal experiments (for example, chloroform, dichlorodiphenyltrichloroethane [DDT], formaldehyde, polychlorinated biphenyls [PCBs], polycyclic aromatic hydrocarbons). Often in the past, direct evidence of human carcinogenicity has come from studies of workplace conditions involving sustained, high-dose exposures. Occasionally, risks are greatly increased when particular exposures occur together (for example, asbestos exposure and cigarette smoking).

Radiation

Only high-frequency radiation—ionizing radiation (IR) and ultraviolet (UV) radiation—has been proven to cause human cancer. Exposure to sunlight (UV radiation) causes almost all cases of basal and squamous cell skin cancer and is a major cause of skin melanoma. Disruption of the earth's ozone layer by atmospheric chemical pollution (the "ozone hole") may lead to rising levels of UV radiation.

Evidence that high-dose IR (x-rays, radon, etc.) causes cancer comes from studies of atomic bomb survivors, patients receiving radiotherapy, and certain occupational groups (for example, uranium miners). Virtually any part of the body can be affected by IR, but especially bone marrow and the thyroid gland. Diagnostic medical and dental x-rays are set at the lowest dose levels possible to minimize risk without losing image quality. Radon exposures in homes can increase lung cancer risk, especially in cigarette smokers; remedial actions may be needed if radon levels are too high.

Unproven Risks

Public concern about environmental cancer risks often focuses on risks for which no carcinogenicity has been proven or on situations where known carcinogen exposures are at such low levels that risks are negligible. For example:

Pesticides. Many kinds of pesticides (insecticides, herbicides, etc.) are widely used in producing and marketing our food supply. Although high doses of some of these chemicals cause cancer in experimental animals, the very low concentrations found in some foods are generally well within established safety levels. However, environmental pollution by slowly degraded pesticides such as DDT, a result of past agricultural practices, can lead to food chain bioaccumulation and to persistent residues in body fat. Such residues have been suggested as a possible risk factor for breast cancer. Studies have shown that

concentrations in tissue are low, however, and the evidence has not been conclusive.

Continued research regarding pesticide use is essential for maximum food safety, improved food production through alternative pest control methods, and reduced pollution of the environment. In the meantime, pesticides play a valuable role in sustaining our food supply. When properly controlled, the minimal risks they pose are greatly overshadowed by the health benefits of a diverse diet rich in foods from plant sources.

Non-ionizing radiation. Electromagnetic radiation at frequencies below ionizing and ultraviolet levels has not been shown to cause cancer. While some epidemiologic studies suggest associations with cancer, others do not, and experimental studies have not yielded reproducible evidence of carcinogenic mechanisms. Low-frequency radiation includes radiowaves, microwaves, and radar, as well as power frequency radiation arising from the electric and magnetic fields associated with electric currents (extremely low-frequency radiation).

Toxic wastes. Toxic wastes in dump sites can threaten human health through air, water, and soil pollution. Although many toxic chemicals contained in such wastes can be carcinogenic at high doses, most community exposures appear to involve very low or negligible dose levels. Clean-up of existing dump sites and close control of toxic materials in the future are essential to ensure healthy living conditions in our industrialized society.

Nuclear power plants. Ionizing radiation emissions from nuclear facilities are closely controlled and involve negligible levels of exposure for communities near such plants. Although reports about cancer case clusters in such communities have raised public concern, studies show that clusters do not occur more often near nuclear plants than they do by chance elsewhere in the population.

Summary of American Cancer Society Recommendations for the Early Detection of Cancer in Asymptomatic People

Site	Recommendation
Cancer-related Checkup	A cancer-related checkup is recommended every 3 years for people aged 20-40 and every year for people age 40 and older. This exam should include health counseling and depending on a person's age, might include examinations for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some nonmalignant diseases.
Breast	Women 40 and older should have an annual mammogram, an annual clinical breast examination (CBE) by a health care professional, and should perform monthly breast self-examination. The CBE should be conducted close to the scheduled mammogram. Women ages 20-39 should have a clinical breast examination by a health care professional every three years and should perform monthly breast self-examination.
Colon & Rectum	Beginning at age 50, men and women should follow *one* of the examination schedules below: • A fecal occult blood test every year and a flexible sigmoidoscopy every five years.* • A colonoscopy every 10 years.* • A double-contrast barium enema every five to 10 years.* *A digital rectal exam should be done at the same time as sigmoidoscopy, colonoscopy, or double-contrast barium enema. People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule.
Prostate	The ACS recommends that both the prostate-specific antigen (PSA) blood test and the digital rectal examination be offered annually, beginning at age 50, to men who have a life expectancy of at least 10 years and to younger men who are at high risk. Men in high-risk groups, such as those with a strong familial predisposition (i.e., two or more affected first-degree relatives), or blacks may begin at a younger age (i.e., 45 years).
Uterus	**Cervix:** All women who are or have been sexually active or who are 18 and older should have an annual Pap test and pelvic examination. After three or more consecutive satisfactory examinations with normal findings, the Pap test may be performed less frequently. Discuss the matter with your physician. **Endometrium:** Women at high risk for cancer of the uterus should have a sample of endometrial tissue examined when menopause begins.

THE AMERICAN CANCER SOCIETY

In 1913, 10 physicians and 5 laymen founded the American Society for the Control of Cancer. Its stated purpose was to disseminate knowledge about the symptoms, treatment, and prevention of cancer; to investigate conditions under which cancer is found; and to compile statistics about cancer. Later renamed the American Cancer Society, Inc., the organization now consists of over 2 million volunteers working to conquer cancer.

Organization: The American Cancer Society, Inc., consists of a National Society with chartered Divisions throughout the country, and more than 3,400 Units.

The National Society: A National Assembly provides basic representation from the Divisions and additional representation on the basis of population. They elect a volunteer Board of Directors who provide leadership in the establishment of organizational goals, ensure management accountability and provide stewardship of the donated funds. The National Society is responsible for overall planning and coordination of the Society's cancer control activities in prevention, detection, and the enhancement of the quality of life of cancer patients and their families. The National Society also provides technical help and materials for Divisions and Units, and administers programs of research, medical grants and clinical fellowships.

The Divisions: These are governed by volunteer members of Division Boards of Directors both medical and lay throughout the US and Puerto Rico.

The Units: Units are organized to deliver cancer control programs in communities throughout the United States. They are led by thousands of local volunteers who direct the activities and programs of the Society at the community level. Descriptions of some of the Society's major programs follow.

ADVOCACY & PUBLIC POLICY

Cancer is a political, as well as a medical, social, psychological, and economic issue. Every day, government policymakers make decisions that affect the lives of more than 8 million cancer survivors, their families, and all potential cancer patients. To impact those decisions positively, the Society has identified advocacy as one of its top corporate priorities and works nationwide to promote beneficial policies, laws, and regulations for those affected by cancer.

Issues and Answers: Cancer-Related Initiatives

In concert with its cancer research, prevention, and control initiatives, the Society's advocacy initiative strives to influence public policies with special emphasis on laws or regulations to:

- Finance cancer initiatives, research in particular
- Ensure access to quality health care
- Reform managed care and protect patients
- Allow scientists to conduct potentially beneficial genetic and bioresearch with appropriate review and controls in place
- Prevent and reduce tobacco use
- Increase access to and participation in clinical trials
- Improve the management of cancer pain and symptoms
- Reduce cancer incidence rates and deaths among the medically underserved
- Provide early detection and treatment options for site-specific cancers

Cancer Resources

The American Cancer Society has identified areas where resource allocation can have an impact on cancer incidence and mortality. These steps begin with cancer prevention, early detection, treatment and research. More resources should be used to prevent cancer as scientific advances allow and as capacity for prevention increases. More funding is needed to answer the public's call for an increased investment in research to further today's knowledge to the next level of cancer breakthroughs. Urging legislative bodies to fund these efforts moves everyone that much closer to our ultimate goal—to defeat cancer.

Advocacy Successes

American Cancer Society advocacy relies on the combined efforts of a community-based grassroots network of Society volunteers, health care professionals, cancer survivors, and other partners who have successfully influenced or supported policies, laws and regulations to:

- Enhance or ensure the role of the US Food and Drug Administration in regulating tobacco products.
- Enact health insurance market reforms to expand coverage and ensure portability and continuity of health insurance coverage for individuals with a history of cancer or other serious illness.
- Broaden the scope of the National Breast and Cervical Cancer Early Detection Program to give medically underserved women the necessary tools needed to fight breast and cervical cancers.

- Institute strong quality standards for clinics providing mammography and ensure patients receive timely and accurate information.
- Increase federal funding for research, prevention and cancer control activities.
- Ensure funds derived from the 1998 multi-state tobacco settlement are at least partially obligated toward tobacco prevention and cessation programs.

The Poor and Underserved

Despite recent progress in the fight against cancer, some Americans continue to bear a disproportionate share of the nation's cancer burden. They include racially and culturally diverse Americans who share characteristics associated with lower levels of income and educational attainment, as well as persons with inadequate medical insurance and individuals who experience barriers because of illiteracy or differing cultural beliefs, practices, and languages.

For almost two decades, the American Cancer Society has engaged in a major initiative to understand and address the needs of these populations who are at high risk for cancer.

The Society's major strategies to address the needs of underserved Americans include:

- Providing local leadership in cancer prevention and control in communities nationwide through collaboration with community-based organizations that address priority interests of the poor and the underserved (such as health, education, spirituality, recreation, and safety).
- Conducting and supporting medical and behavioral research to discover effective cancer prevention practices, early detection measures and treatments among high-risk populations.
- Advocating at all levels of government for public policies, funding and leadership that will reduce disparities in cancer incidence and mortality. This includes advocacy for tobacco control, comprehensive school health education, and access to health care.

Cancer Information

Providing the public with accurate, up-to-date information on cancer is a priority for the American Cancer Society. The Society provides information on all aspects of cancer through a toll-free information line, web site, and published materials.

National Cancer Information Center 1-800-ACS-2345

People facing cancer need clear, reliable information in order to understand their disease and make informed decisions about their health. Trained cancer information specialists are available 24 hours a day, seven days a week to answer questions about cancer, link callers with resources in their communities, and provide information on local events. Callers who speak languages other than English and Spanish can also be assisted. The National Cancer Information Center includes an email response center staffed by cancer information specialists who respond to questions and comments submitted through the Society's web site.

American Cancer Society Web Site www.cancer.org

The Internet is an important resource for people seeking information about cancer. The American Cancer Society's web site is an important extension of the Society's mission to provide lifesaving information to the public. The user-friendly site includes an interactive cancer resource center containing in-depth information on every major cancer type. Through the resource center, visitors can order American Cancer Society publications, gain access to recent news articles, and find additional on- and off-line resources. Other useful sections on the web site include a directory of medical resources, links to other sites organized by cancer type or topic, resources for media representatives, and information on the Society's research grants program, advocacy efforts, and special events.

Publications

The Society publishes a large number of patient education brochures and pamphlets, books, and professional journals to help patients, families, and health care professionals. These include books on specific cancer types, coping issues, and prevention; cookbooks; and textbooks and other specialized cancer-related topics for health care professionals. Four clinical journals (*Cancer, Cancer Cytopathology, CA-A Cancer Journal for Clinicians,* and *Cancer Practice*) are also available. For more information, call 1-800-ACS-2345 or visit our online bookstore at www.cancer.org.

Community Cancer Control

Community cancer control encompasses activities at the local, state, regional, or national level, which have a positive impact on the entire spectrum of prevention, early detection, effective treatment, survival, and quality of life related to cancer. Across the country, the Society seeks to fulfill its mission to save lives and diminish suffering from cancer through community-based programs aimed at reducing the risk of cancer, detecting cancer as early

as possible, ensuring proper treatment, and empowering people facing cancer to cope with the disease and maintain the highest possible quality of life.

Prevention

Primary cancer prevention means taking the necessary precautions to prevent the occurrence of cancer in the first place. The Society's prevention programs focus primarily on tobacco control, the relationship between diet and physical activity and cancer, promoting coordinated school health, and reducing the risk of skin cancer. Programs are designed to help adults and children make health-enhancing decisions and act on them.

The Society has joined other health, education, and social service agencies to promote comprehensive school health education and National School Health Education Standards. Comprehensive school health education is a planned health education curriculum for pre-school to Grade 12. The Standards describe for schools, parents, and communities how to create an instructional program that will enable students to become healthy and capable of academic success.

The Society's school health education programs emphasize the importance of developing good health habits and can be an integral part of a comprehensive school health education curriculum.

The Society promotes its skin protection message through a variety of media and education activities, as well as through the 33-member organizations of the American Cancer Society Skin Protection Federation. This coalition includes non-profit organizations, government agencies, and corporations that have a combined constituency of over 100 million adults and children. The purpose of the coalition is to accelerate promotion of the American Cancer Society's guidelines for skin cancer prevention, and to provide a forum for member organizations to share information and strategies that increase awareness about skin protection and encourage more people to adopt skin protection behaviors.

Detection and Treatment

The Society also seeks, through the dissemination of its early detection guidelines and its detection education and advocacy programs, to ensure that cancer is diagnosed at the earliest possible stage, when there is the greatest chance for successful treatment. The Society works in partnership with many public and private sector organizations in diverse settings to increase awareness about breast cancer and the importance of early detection, and to overcome the barriers to regular mammography use.

The Society, in partnership with the Centers for Disease Control and Prevention, is leading a national initiative to increase colorectal cancer screening, now greatly underused. (For more information about American Cancer Society screening guidelines, see p. 34.)

The availability of genetic testing for inherited risk for cancer has raised a complex set of questions about the medical, psychosocial, ethical, legal, policy, and quality-of-life implications of genetic information. The Society is working with other national organizations to address these issues through advocacy and educational initiatives.

As the delivery of health care continues to change, the Society is working with partners in all sectors of the health care system to ensure that all individuals are offered a full range of preventive services to enable them to reduce their risk of getting cancer or to find their cancer at an early, treatable stage, and that persons with cancer receive the highest quality care.

Patient Services

Patient support is the range of emotional and practical help the Society offers for patients, their families, their caregivers, and their community from the time of diagnosis throughout life to life's end:

Reach to Recovery: A visitation program for women and their families who have a personal concern about breast cancer. Trained volunteers who have experienced breast cancer themselves provide information and support. The *Early Support* program provides visitors who are positive role models (breast cancer survivors who can provide support to other women).

"tlc": A service offering of the Society, *"tlc"* is a "magalog" designed to provide needed medical information and special products for women newly diagnosed with breast cancer and breast cancer survivors. The magalog features articles which focus on medical questions specific to breast cancer, and also has a Question & Answer section. *"tlc"* features a variety of hats, honeys, caps, turbans, hairpieces, swimwear, bras, prostheses, and breast forms. Many products are also appropriate for any woman experiencing treatment-related hair loss. Free copies are available by calling 1-800-850-9445.

Look Good...Feel Better: In partnership with the Cosmetic, Toiletry and Fragrance Association Foundation and the National Cosmetology Association, this free program is designed to teach women cancer patients beauty techniques to help restore their appearance and self-image during chemotherapy and radiation treatments.

Man to Man: This group program provides information about prostate cancer and related issues to men and their partners in a supportive atmosphere. Some areas offer *Side by Side,* a group program for the partners of men with prostate cancer, and/or a visitation program in which a trained prostate cancer survivor provides support to a man newly diagnosed with prostate cancer.

Children's Camps: In some areas, the Society sponsors camps for children who have, or have had, cancer. These camps are equipped to handle the special needs of children undergoing treatment.

Hope Lodge: Housing is provided in some areas through funds raised specifically to purchase a dwelling to house patients during their treatment; 16 lodges are in operation.

I Can Cope: This patient and family cancer education program consists of a series of classes, often held at a local hospital. Doctors, nurses, social workers, and community representatives provide information about cancer diagnosis and treatment, as well as assistance in coping with the challenges of a cancer diagnosis.

RESEARCH

The American Cancer Society is the largest source of private, not-for-profit cancer research funds in the US, second only to the federal government in total dollars spent. In fiscal year 1998, the Society invested over $100 million in research. To date, the Society has invested more than $2 billion in cancer research. The research program consists of three components: extramural grants, intramural epidemiology and surveillance research, and the intramural behavioral research center.

Extramural Grants

The extramural program supports investigator-initiated projects taking place in leading centers across the country, as well as training grants in selected health professions. Applications for grants are subjected to a rigorous external peer review which ensures that only the highest quality applications receive funding. The success of the Society's research program is exemplified by the fact that 30 Nobel Prize winners received grant support from the Society early in their careers.

Epidemiology and Surveillance Research

Intramural epidemiologic research at the Society publishes descriptive information about trends in cancer incidence, cancer mortality, cancer risk factors, and cancer patient care, and studies the causes and prevention of cancer in large prospective studies. For the past two years, the department has collaborated with the National Cancer Institute and the Centers for Disease Control and Prevention, including the National Center for Health Statistics to produce the *Report to the Nation* on progress related to cancer prevention and control in the United States.

The department also analyzes patterns of cancer causation in large prospective studies. Three such studies have been undertaken over the past 50 years:

- Hammond-Horn (188,000 men studied from 1952–1955)
- Cancer Prevention Study I (1 million people studied from 1959–1972 in 25 states)
- Cancer Prevention Study II (CPS II, a continuing study of 1.2 million people enrolled in 1982 by 77,000 volunteers in 50 states)

Over 100 scientific publications based on CPS-II have examined the contribution of lifestyle (smoking, nutrition, weight, etc.,) family history, illnesses and medications, and environmental exposures to various cancers. Of particular interest is how diet and changes in diet and physical activity affect cancer. To examine this, questionnaire information on 184,000 participants is updated every 2–3 years. Another component of CPS II, LifeLink, will collect and store blood specimens from 30,000-65,000 of these participants for future studies on the effects of nutritional factors, hormones, and genetic susceptibility on cancer risk.

Behavioral Research Center

The Center was established in 1995 to conduct original behavioral and psychosocial cancer research, provide consultation to other parts of the Society, and facilitate the transfer of behavioral and psychosocial research and theory to improve cancer control policies. Among the ongoing research projects of the Center are:

- A nationwide, longitudinal study of 100,000 adult cancer survivors to determine the unmet psychosocial needs of survivors and their significant others, to identify factors that affect their quality of life, to evaluate programs intended to meet their needs, and to examine late effects including second cancers.
- A cross-sectional study of 2-, 5-, and 10-year cancer survivors to evaluate their psychological needs, adjustment, and quality of life.
- A study of the knowledge, attitudes, and behaviors of a managed-care population regarding colorectal cancer screening.
- A longitudinal study of the use of stage-based smoking cessation materials implemented in conjunction with the Society's Cancer Control Department and the National Cancer Information Center.
- A series of studies of the risk perceptions and behavioral characteristics of cigar smokers to better understand the increase in US cigar smoking.

SOURCES OF STATISTICS

Cancer Deaths. The estimated numbers of US cancer deaths are calculated by fitting the numbers of cancer deaths for 1979 through 1997 to a statistical model which forecasts the numbers of deaths that are expected to occur in 2000. The estimated numbers of cancer deaths for each state are calculated similarly, using state level data. For both the US and state estimates, data on the numbers of deaths are obtained from the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention.

We discourage the use of our estimates to track year-to-year changes in cancer deaths because the numbers can vary considerably from year to year, particularly for less common cancers and for smaller states. Mortality rates reported by NCHS are generally more informative statistics to use when tracking cancer mortality trends.

Mortality Rates. Mortality rates or death rates are defined as the number of people per 100,000 dying of a disease during a given year. In this publication, mortality rates are based on counts of cancer deaths compiled by NCHS for 1973 through 1997 and population data from the US Bureau of the Census.

New Cancer Cases. The estimated numbers of new US cancer cases are calculated by estimating the numbers of cancer cases that occurred each year for 1979 through 1996 and fitting these estimates to a statistical model which forecasts the numbers of cases that are expected to occur in 2000. Estimates of the numbers of cancer cases for 1979 through 1996 are used rather than actual case counts because case data are not available for all 50 states. The estimated numbers of cases for 1979 through 1996 are calculated using cancer incidence rates from the regions of the United States included in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and population data collected by the US Bureau of the Census.

State case estimates cannot be calculated using the same modeling strategy that we use to calculate state death estimates. Instead, estimates are calculated using cancer deaths forecasted for each state for 2000 and US estimates of new cancer cases and cancer deaths for 2000.

Like the method used to calculate cancer deaths, the methods used to estimate new US and state cases for the upcoming year can produce numbers that vary considerably from year to year, particularly for less common cancers and for smaller states. For this reason, we discourage the use of our estimates to track year-to-year changes in cancer occurrence. Incidence rates reported by SEER are generally more informative statistics to use when tracking cancer incidence trends for the total United States, and rates from state cancer registries are useful for tracking local trends.

Incidence Rates. Incidence rates are defined as the number of people per 100,000 who develop disease during a given time period. For this publication, incidence rates were calculated using data on cancer cases collected by the SEER program and population data collected by the US Bureau of the Census. State incidence rates presented in this publication were originally published in the North American Association of Central Cancer Registries' publication Cancer Incidence in North America, 1991-1995. Incidence rates for the United States were originally published in the *SEER Cancer Statistics Review, 1973-1996.*

Survival. Five-year relative survival rates are presented in this report for cancer patients diagnosed between 1989 and 1995 and followed through 1996. To adjust for normal life expectancy (factors such as dying of heart disease, accidents, and diseases of old age), these rates are calculated by dividing 5-year survival rates for cancer patients by 5-year survival rates for people in the general population who are similar to the patient group with respect to age, gender, race, and calendar year of observation. All survival statistics presented in this publication were originally published in the *SEER Cancer Statistics Review, 1973-1996.*

Probability of Developing Cancer. Probabilities of developing cancer are calculated using DEVCAN (Probability of DEVeloping CANcer Software) developed by the National Cancer Institute. These probabilities reflect the average experience of people in the United States and do not take into account individual behaviors and risk factors. For example, the estimated 1 man in 1,200 likely to develop lung cancer is a low estimate for smokers and a high estimate for nonsmokers.

Additional Information. More information on the methods used to generate the statistics for this report can be found in the following publications:

A. For information on data collection methods used by the National Center for Health Statistics: National Center for Health Statistics. *Vital Statistics of the United States, 1997, Vol II, Mortality, Part A.* Washington: Public Health Service. 1999.

B. For information on data collection methods used by the National Cancer Institute's Surveillance, Epidemiology and End Results Program: Ries LAG, Kosary CL, Hankey BF, et al. (eds.). *SEER Cancer Statistic Review, 1973-1996.* National Cancer Institute. Bethesda, MD, 1999 or visit the SEER web site at www-seer.ims.nci.nih.gov.

C. For information on the methods used to estimate the numbers of new cancer cases and deaths: Wingo PA, Landis S, Parker S, Bolden S, Heath CW. Using cancer registry and vital statistics data to estimate the number of new cancer cases and deaths in the Unites States for the upcoming year. *J Reg Management* 1998;25(2):43-51.

D. For information on the methods used to calculate the probability of developing cancer: Feuer EJ, Wun L-M, Boring CC et al. The lifetime risk of developing breast cancer. *JNCI* 1993; 85:892-897.

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GERM CELL TUMORS OF THE OVARY

Germ cell tumors of the ovary are much less common than epithelial ovarian neoplasms. However, because they are more highly curable and because they affect primarily young women of childbearing potential, appropriate management by specialists is exceedingly important. Germ cell tumors account for 2% to 3% of all ovarian cancers in Western countries. They almost always occur in younger women and their peak incidence is in the early 20s. In Asian and Black societies, there is an increased incidence of germ cell tumors and they represent as many as 15% of all ovarian cancers in these populations. [ref: 363]

Leslie Bernstein, Malcolm A. Smith, Lihua Liu, Dennis Deapen, Debra L. Friedman

HIGHLIGHTS

Incidence

- While germ cell, trophoblastic and other gonadal (GCTOG) tumors represented 16% of all cancers among adolescents between 15 and 19, they represented only 7% of cancer diagnoses among children younger than 20 (incidence 12.0 per million) and 3.5% of cancer diagnoses for children younger than 15 (incidence 5.4 per million) (Table X.4).
- In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year.
- The majority (61%) of GCTOG tumors occurring among children younger than 20 years are gonadal (ovarian or testicular) germ cell tumors (Table X.1). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors are more common than gonadal germ cell tumors (Table X.4).
- For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per million, and then declined to very low levels by age 4. Between ages 4 and 15 the rates of testicular germ cell tumors remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically (Figure X.2).
- For females, ovarian (gonadal) germ cell tumors (Xc) began to increase in incidence at age 8-9 years and peaked at age 18 (20 per million) (Figure X.3). For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million).
- White males younger than age 20 had much higher rates of testicular germ cell tumors (9.1 per million) than blacks males (1.2 per million). In contrast, white females younger than age 20 had slightly lower rates (4.5 per million) than black females (5.6 per million) for ovarian germ cell tumors (Table X.3).

Survival

- For patients younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks for GCTOG tumors (Figure X.6).
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 (Figure X.7). The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6).
- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors. Both increased from 82% to 93-94% (Figure X.7). Young males (<5 years) survived better than males aged 15-19.

Risk factors

- The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references).

INTRODUCTION

Germ cell tumors are biologically diverse and histologically heterogeneous [1-3], with a substantial proportion having benign rather than malignant behavior (particularly among young children). Germ cell tumors originate in primordial germ cells, which may undergo germinomatous or embryonic differentiation. Primordial germ cells are initially detectable in the yolk sac of the four week embryo, and their migratory route during embryogenesis from the yolk sac to the gonads (either the testes or ovaries) may account for the primarily midline location of most extragonadal germ cell tumors [1].

Germ cell tumors are grouped together with trophoblastic and other gonadal neoplasms in the International Classification of Childhood Cancer (ICCC) [4]. For shorthand notation this entire group, ICCC X, will be abbreviated as GCTOG tumors. This diagnostic group is categorized into five subgroups according to the cells of origin of the cancer (germ cells, trophoblastic cells or other cells) and the location in the body of the cancer (gonads: testes or ovaries; central nervous system; or elsewhere) (see Table X.1).

In the US, approximately 900 children and adolescents younger than 20 years of age are diagnosed with germ cell tumors each year. Essential for understanding the incidence patterns for germ cell tumors of children and adolescents is recognition that the germ cell tumors of infancy and early childhood are biologically distinctive from those that arise in older children and adolescents [2,3]. Thus, tumors in the same ICCC subgroup may have very different biological characteristics and clinical behavior (Table X.2. [5]). The categorization of germ cell tumors in Table X.2 provides a

Table X.1: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by sex and subtype, age <20 all races, SEER, 1986-95

ICCC Group X	Description	Total	Males	Females
X a-e	Germ cell, trophoblastic and other gonadal tumors	11.6	12.0	11.1
Xa	Intracranial and intraspinal germ cell tumors	1.6	2.3	0.9
Xb	Other and unspecified non-gonadal germ cell tumors. (This category includes the tumors of infants and young children that originate in the sacrococcygeal region, as well as mediastinal tumors primarily developing in older children.)	1.6	1.5	1.8
Xc	Gonadal germ cell tumors	6.7	8.0	5.3
	Testis	4.1	8.0	-
	Ovary	2.6	-	5.3
Xd	Gonadal carcinoma	1.4	0.1	2.9
	Ovary	1.3	-	2.6
	Other	0.1	0.1	0.3
Xe	Other and unspecified malignant gonadal tumors	0.2	0.1	0.3

*Adjusted to the 1970 US standard population

Table X.2: GCTOG tumors by sub-group, age and biological characteristics [5]

GCTOG TUMORS (ICCC X)	Site	Age	Characteristics
Intracranial and intraspinal germ cell tumors (ICCC Xa)	Intracranial (especially pineal region) [2]	Older children, adolescents and adults	Some, though not all, of these tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [6-9].
Non-CNS, Non-gonadal germ cell (ICCC Xb)	Sacrococcygeal/pelvic region [2]	Infants and young children	The biological characteristics of these tumors is similar to those of testicular germ cell tumors in young boys (see below), but different from those of testicular germ cell tumors in adolescents and young adults (see below).
"	Mediastinum [2]	Older children, adolescents and adults	Some, though not all, mediastinal germ cell tumors have biological characteristics similar to those of testicular germ cell tumors in adolescents and young adults (e.g., an isochromosome of the short of chromosome 12 as discussed below) [10,11].
Gonadal germ cell (ICCC Xc)	Testicular	Infants and young boys	The biological characteristics of these tumors are distinctive from those of testicular germ cell tumors in adolescents and young adults (see below). The tumors primarily show yolk sac tumor (endodermal sinus tumor) histology and are generally diploid or tetraploid. Recurring chromosomal abnormalities include deletions of chromosome 1p and 6q, but not isochromosome of the short arm of chromosome 12 [12-15].
"	Testicular	Adolescents and young adults	These typically possess an isochromosome of the short arm of chromosome 12 [5,16-19] and are aneuploid [12,19]
"	Ovary	Adolescents and adults	These show greater biological diversity than do germ cell tumors arising in the testes, and include malignant teratomas and other malignant germ cell tumors (e.g., dysgerminomas, yolk sac tumors, and mixed germ cell tumors). Like their testicular counterparts, they commonly show increased copies of the short arm of chromosome 12 [5].
Gonadal carcinomas (Xd)	Ovary	Adolescents and adults	These carcinoma tumors are not biologically related to the germ cell tumors and develop almost exclusively in the ovary.

basis for understanding the incidence patterns and trends of germ cell tumors in children.

A total of 2,065 children younger than 20 years of age were diagnosed with GCTOG tumors during the period 1975 through 1995 in the SEER areas. This represents 7% of all neoplasms diagnosed among children younger than 20 years of age: 3.5% of all neoplasms for children younger than 15 years of age and a much higher proportion, 13.9%, for 15-19 year olds. The majority (1,260 or 61%) of GCTOG tumors occurring among children younger than 20 years of age are gonadal (ovarian or testicular) germ cell tumors (Xc). However, when only children younger than 15 years of age are considered, non-gonadal germ cell tumors (Xa and Xb) are more common than gonadal germ cell tumors.

The GCTOG tumor group (ICCC X) includes 94% of the malignant testicular tumors and 99% of the ovarian tumors among children and adolescents. Six percent of malignant testicular tumors and less than 1% of ovarian tumors are sarcomas and are grouped under ICCC IX (soft tissue sarcomas). Excluding the sarcomas, nearly all of the testicular tumors in male children and adolescents were germ cell tumors, 98%. Excluding the small number of ovarian sarcomas, the histologic types of ovarian tumors in female children and adolescents were 64% germ cell (Xc), 33% carcinomas (Xd), and 3% other and unspecified (Xe).

INCIDENCE

Sex-specific incidence

Table X.1 shows the incidence of GCTOG tumors by sex for children younger than 20 years of age for the years 1986 to 1995. The incidence for males (12.0 per million) slightly exceeded that for females (11.1 per million). For males, the subgroup with the highest incidence was testicular germ cell tumors (8.0 per million). For females, ovarian germ cell tumors had the highest rate (5.3 per million). Intracranial and intraspinal germ cell tumors (ICCC Xa) were more common in males (2.3 per million) than in females (0.9 per million), and accounted for about 14 percent of all GCTOG tumors among those younger than 20 years of age. Non-gonadal germ cell tumors arising outside of the central nervous system (CNS), ICCC Xb, occurred with similar frequency among males and females. In contrast gonadal carcinomas were almost exclusively seen among females and most of these were ovarian gonadal carcinomas.

Table X.3: Average annual age-adjusted* incidence rates per million for germ cell trophoblastic and other gonadal cancers by race, sex, and subtype age <20, SEER, 1975-95

ICCC Group X	ICCC Germ Cell Tumor Category	White Male	Black Male	White Female	Black Female
X a-e	All	12.3	3.2	9.0	10.8
Xc	Gonadal germ cell tumors	9.1	1.2	4.5	5.6
	Testis	9.1	1.2	-	-
	Ovary	-	-	4.5	5.6
X a,b,d,e	Other than gonadal germ cell tumors	3.2	2.0	4.5	5.2

*Adjusted to the 1970 US standard population

Black-white differences in incidence

Black children had a lower incidence of germ cell tumors than white children (7.0 vs. 10.7 per million). This difference was primarily the result of a lower rate of gonadal germ cell tumors among blacks than whites. Table X.3 shows the incidence rates for gonadal germ cell tumors for children younger than 20 years of age for the years 1975 to 1995 by race and sex. Remarkably, the lower rates of gonadal germ cell tumors among black children were restricted to males. For children younger than 20 years of age, black males had a rate of testicular germ cell tumor that was only one-seventh that for white males (1.2 versus 9.1 per million), while black females had slightly higher rates of ovarian germ cell tumors than white females (5.6 versus 4.5 per million). The low rate of testicular germ cell tumors observed among young black males is consistent with the reported low incidence for testicular cancer among adult black males [20-22].

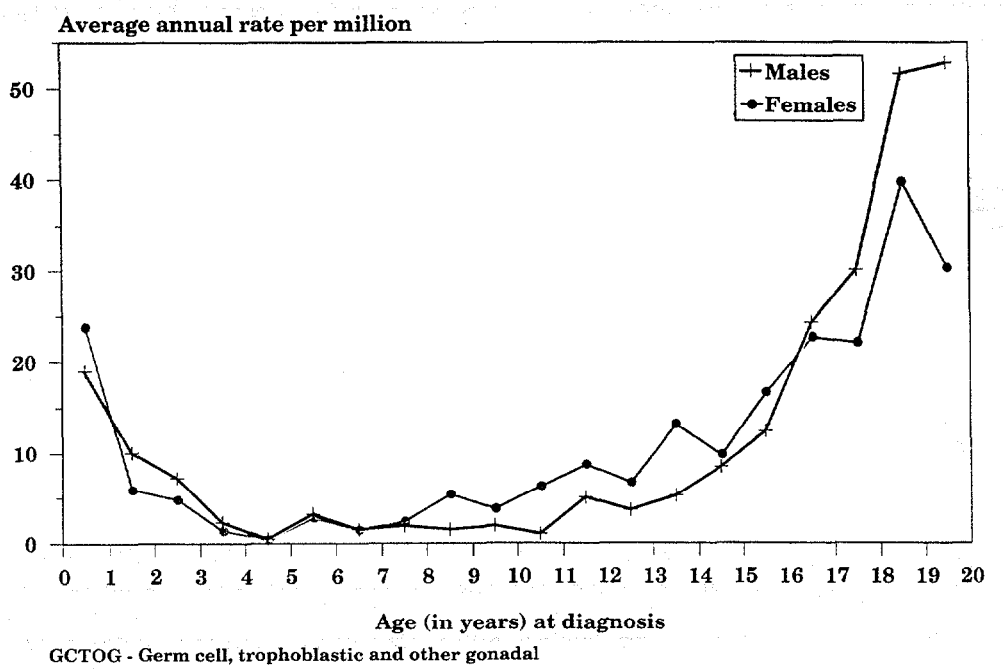
Age-specific incidence

Figure X.1 shows the age-specific incidence of GCTOG tumors by single year of age and sex.[1] Rates were relatively high in the first year of life and then declined to very low levels before increasing at age 8-12 years for females and at age 11-14 years for males. Incidence continued to increase for both males and females up through age 19. The distribution of tumor types by age was distinctive for males and females.

For males, the incidence rates of testicular (Xc) and non-CNS extragonadal (Xb) germ cell tumors were similar during the first year of life at approximately 9 per

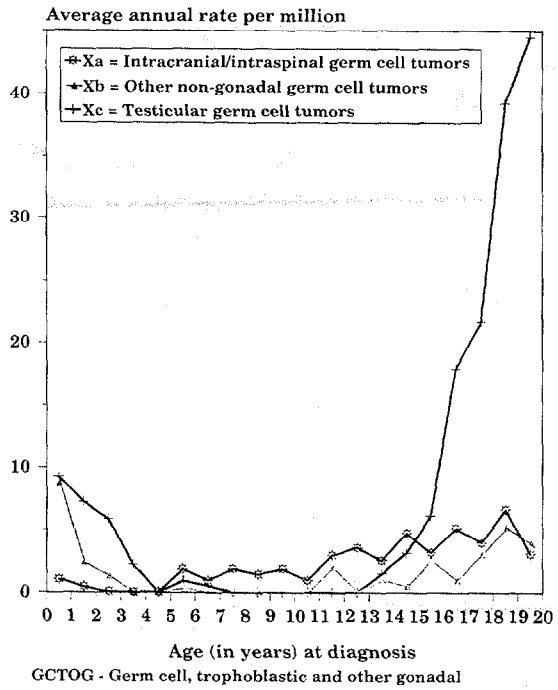
[1] Enumeration of the population at risk by single years of age was available only for the census year 1990. The US Bureau of the Census provides intercensal population estimates by 5-year age groups, but not by single years of age. Therefore, the population estimates for 1990 were used in rate calculations for cases diagnosed from 1986-94.

Figure X.1: GCTOG age-specific incidence rates by sex, all races, SEER, 1986-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.2: GCTOG age-specific incidence rates by selected ICCC subgroups, males all races, SEER, 1986-94



million, and then declined to very low levels by age 4 years (Figure X.2). Between ages 4 and 15 the rates remained very low, but between ages 15 and 19 years of age, the incidence rates increased dramatically.

For females, non-CNS extragonadal germ cell tumors (Xb) accounted for the vast majority of cases in the first year of life, with ovarian germ cell tumors (Xc) being extremely rare (Figure X.3). Most of the extragonadal germ cell tumors arising in the first year of life occurred in pelvic soft tissue (e.g., the sacrococcygeal region) and in the retroperitoneum. Gonadal germ cell tumors (Xc) began to increase in incidence for females at age 8-9 years, while gonadal carcinomas (Xd) began to increase after age 12. By age 19, the rate of gonadal carcinomas (Xd) was similar to ovarian germ cell tumors (Xc) in females. For males, the rate of testicular germ cell tumors (Xc) at age 19 was substantially higher than that observed for ovarian germ cell tumors among 19 year old females (44.5 versus 10.4 per million for age 19).

TRENDS

The age-adjusted incidence rates for GCTOG tumors increased between 1975-79 and 1990-95 from 3.7 to 5.4 per million for children younger than 15 years of age and from 8.5 to 12.0 per million for those younger than 20 years of age (Table X.4). For both males and females younger than 15 years of age, the increase in incidence primarily resulted from higher rates for intracranial and intraspinal germ cell tumors (Xa) and for non-CNS extragonadal germ cell tumors (Xb), while the rates of gonadal germ cell tumors (Xc) did not increase. The increased incidence of non-CNS extragonadal tumors (Xb) for both males and females was due in large measure to an increase in incidence in the first

Figure X.3: GCTOG age-specific incidence rates by selected ICCC subgroups females, all races, SEER, 1986-94

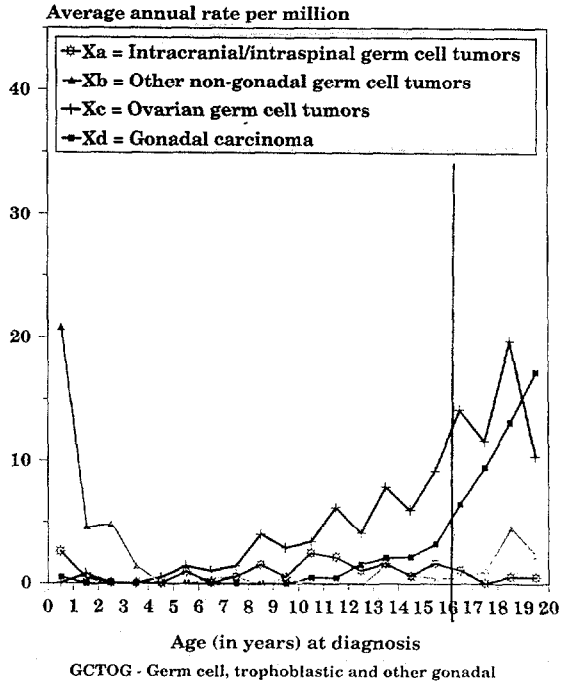


Table X.4: Average annual age-adjusted[1] incidence rates per million for germ cell trophoblastic, and other gonadal cancers by sex, age, subtype, and time period, all races, SEER, 1975-95

Sex/Age Group	Years	X(total)	Xa[2]	Xb[2]	Xc[2]	Xd[2]	Xe[2]
Total <15	1975-79	3.7	0.5	0.7	2.2	0.1	0.2
	1980-84	4.8	0.9	1.1	2.6	0.1	0.1
	1985-89	4.8	0.7	1.3	2.7	0.1	0.1
	1990-95	5.4	1.5	1.4	2.1	0.3	0.0
Males <15	1975-79	3.1	0.5	0.6	1.8	0.1	0.1
	1980-84	4.1	1.2	0.9	2.0	0.0	0.0
	1985-89	4.1	1.1	0.8	2.2	0.0	0.1
	1990-95	4.4	1.9	1.1	1.4	0.0	0.0
Females <15	1975-79	4.3	0.4	0.8	2.6	0.2	0.4
	1980-84	5.5	0.6	1.3	3.3	0.2	0.2
	1985-89	5.6	0.4	1.8	3.2	0.1	0.1
	1990-95	6.4	1.2	1.9	2.7	0.7	0.0
Total <20	1975-79	8.5	0.6	1.4	5.4	0.8	0.3
	1980-84	9.6	0.9	1.5	6.4	0.7	0.2
	1985-89	10.7	1.1	1.7	6.6	1.1	0.2
	1990-95	12.0	1.9	1.6	6.8	1.6	0.2
Males <20	1975-79	9.1	1.0	1.2	6.9	0.1	0.1
	1980-84	11.0	1.2	1.5	8.1	0.1	0.1
	1985-89	11.4	1.7	1.6	7.8	0.1	0.1
	1990-95	12.2	2.6	1.3	8.1	0.1	0.1
Female <20	1975-79	7.8	0.3	1.6	3.9	1.5	0.6
	1980-84	8.1	0.6	1.5	4.5	1.3	0.3
	1985-89	10.0	0.4	1.8	5.3	2.2	0.3
	1990-95	11.7	1.1	1.8	5.3	3.2	0.3

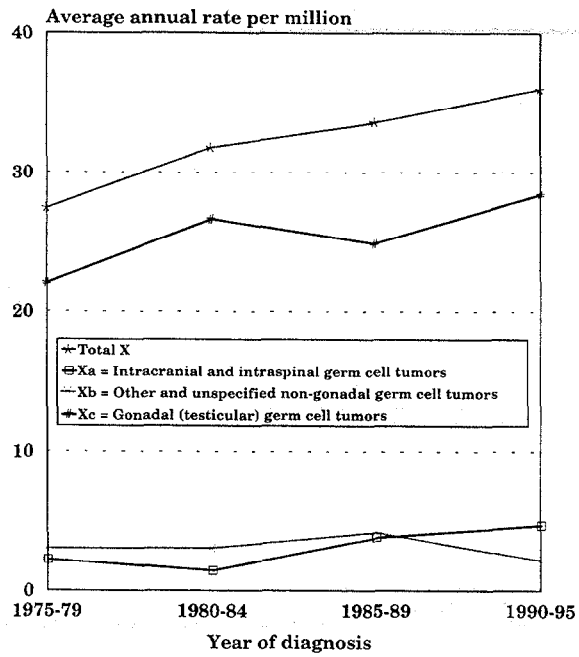
[1] Adjusted to the 1970 US standard population

[2] Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe = Other and unspecified malignant gonadal tumors.

year of life. This increase in non-CNS extragonadal malignant tumors among infants must be interpreted with caution, because non-malignant sacrococcygeal teratomas diagnosed in the newborn period outnumber malignant teratomas [3,23-25], and because careful inspection of mature and immature sacrococcygeal teratomas may show microscopic foci of yolk sac tumor [26,27]. Since nonmalignant sacrococcygeal teratomas are not reported and yolk sac tumors are reported, the increase in incidence in the first year of life may be the result of increasing recognition by pathologists of the need for careful scrutiny of apparently non-malignant sacrococcygeal teratomas. Almost all of the increase in the first year of life for females was in malignant teratomas/embryonal teratomas.

An increase in the age-adjusted incidence for GCTOG tumors was also observed for both sexes among those younger than 20 years of age. For males younger than 20 years of age, the increase in incidence was from 9.1 to 12.2 per million, with most of the increase attributed to intracranial and intraspinal germ cell tumors (Category Xa) and to testicular germ cell tumors (Category Xc). For females, the increase was from 7.8 to 11.7 per million, with most of the increase attributable to ovarian germ cell tumors

Figure X.4: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, males, all races, SEER 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

(Category Xc) and to ovarian carcinomas (Category Xd). Because of the larger number of cases in the 15-19 year group compared to the younger than 15 year group, the trends for those younger than 20 years of age are primarily determined by trends for the 15-19 year age group.

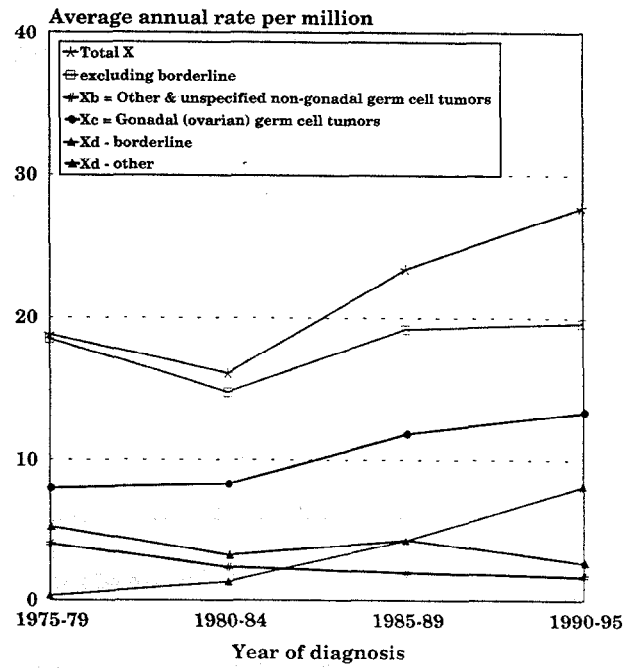
Figure X.4 illustrates the increase in incidence of testicular germ cell tumors (Xc) for the 15-19 year age group between 1975-79 (22 per million) and 1990-1995 (28 per million). The increase in incidence of testicular germ cell tumors for those 15-19 years of age is reminiscent of the increase in testicular cancer among adult males. Over the past 30-40 years, increased rates of testicular cancer have been reported from developed countries throughout the world, including the United States [21,22], European countries [28], Australia [29], and New Zealand [30].

The overall rate of GCTOG tumors for females aged 15-19 increased markedly from 1975-79 to 1990-95 (Figure X.5), but much of the increase was attributable to the inclusion of borderline tumors of the ovary which were not reportable cancers for the entire time period. Figure X.5 shows the overall rate for ICCC X for females both with and without the borderline tumors. With the borderline tumors excluded, the overall rate increased only slightly between 1975-79 and 1990-95 (Figure X.5), and this increase was driven by an increased incidence of ovarian germ cell tumors (8 per million for 1975-79 to 13 per million for 1990-95). An increased incidence for ovarian germ cell tumors in adults has also been reported [31,32].

SURVIVAL

For the period from 1985 to 1994, the 5-year survival rate for patients

Figure X.5: Trends in GCTOG age-specific incidence rates by selected ICCC subgroups age 15-19, females, all races, SEER, 1975-95



GCTOG - Germ cell, trophoblastic and other gonadal

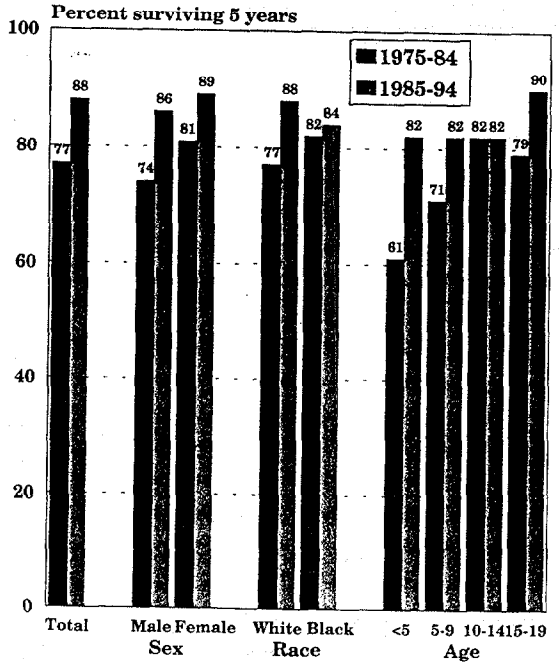
younger than 20 years of age with germ cell tumors was 87% (Figure X.6). Survival rates were better for the 15-19 year olds (5-year survival, 90%) than for the younger than 15 year olds (5-year survival, 84%). Other observations about outcome for children with germ cell tumors are illustrated in Figures X.6 and X.7 and include:

- For those younger than 20 years of age, females had slightly higher 5-year survival rates than males, and whites had somewhat higher 5-year survival rates than blacks (Figure X.6).

- Survival for patients younger than 20 years of age was better for gonadal germ cell tumors (ICCC Xc) than for tumors arising at "other and unspecified" sites (ICCC Category Xb), with 5–year survival rates of 94% and 71%, respectively in 1985-1994. Outcome was similar for patients younger than 20 years of age with intracranial germ cell tumors (ICCC Xa) and with tumors arising at "other and unspecified" sites (ICCC Xb), with both groups having survival rates for 1985-94 of approximately 70% (Figure X.7).

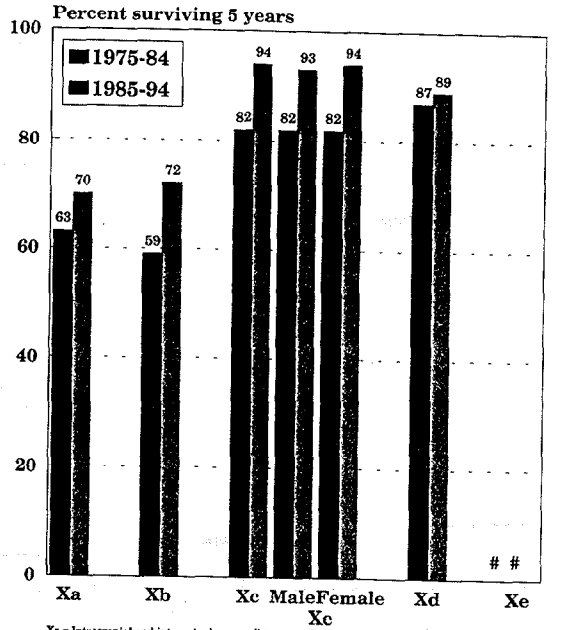
- Increasing survival rates were observed between 1975-84 and 1985-94 for each subgroup of the ICCC for patients younger than 20 years if age. The overall 5-year relative survival rate for all subgroups combined increased from 77% to 87% (Figure X.6). The largest increase in survival was for tumors arising at other and unspecified sites (ICCC Xb): 58 percent compared to 72 (Figure X.7).

Figure X.6: Germ-cell tumor 5-year relative survival rates by sex, race, age, and time period SEER (9 areas), 1975-84 and 1985-94



GCTOG - Germ cell, trophoblastic and other gonadal

Figure X.7: GCTOG tumor 5-year relative survival rates by sub-group, sex and time period, all races SEER (9 areas), 1975-84 and 1985-94



Xa = Intracranial and intraspinal germ cell tumors; Xb = Other and unspecified non-gonadal germ cell tumors; Xc = Gonadal (ovarian and testicular) germ cell tumors; Xd = Gonadal carcinoma; Xe - Other and unspecified malignant gonadal tumors.

GCTOG - Germ cell, trophoblastic and other gonadal # - < 25 cases - rate not shown

Table X.5: Current knowledge on causes of childhood malignant germ cell tumors (MGCT)

Exposure or Characteristic	Comments	References
Known risk factors		
Cryptorchidism	Risk is increased 2.5 - 11-fold. The contralateral as well as ipsilateral testis is at increased risk.	34-36
Factors for which evidence is suggestive but not conclusive		
High maternal hormone levels during pregnancy	Use of oral contraceptives during pregnancy, high pre-pregnancy weight, bleeding, hyperemesis and spotting indicate high hormone levels.	34,35,37-39
Family history of germ cell tumor	When malignant germ cell tumors occur in the same family, they are usually of the same histologic type.	40,41
Hernia	Central nervous system and genitourinary anomalies have also been observed in germ cell tumor patients.	34,35,42
Pre-term birth	Excess risk was not explained by cryptorchidism.	43,44
Trauma	The causality of this association is not clear. Trauma may result in closer scrutiny and earlier detection of an existing tumor.	45-47
Factors for which evidence is inconsistent or limtied		
Virus infection, e.g., mumps, cytomegalovirus, Epstein-B virus, and parvovirus B19		48-52
High birth weight		35,43,44
Prenatal X-ray exposure		43,53
Parental occupation	Associations have been observed with maternal employment in the medical field, paternal employment in service stations and aircraft industry, and paternal exposure to x-rays, maternal exposure to solvents, plastic and resin fumes.	44,54,55
Constitutional chromosome abnormalities, particularly sex chromosome abnormalities (e.g., Klinefelter syndrome (47,XXY), inverted Y)		56-60

The increase in survival for this subgroup, ICCC Xb, was dramatic for children younger than 5 years of age; the survival rate increased from 38% to 86%.

- The increase in survival between 1975-84 and 1985-94 was similar for ovarian and testicular germ cell tumors (Figure X.7). Both increased from 82% to 93-94%.

The improvement in outcome observed in the more recent period for children with germ cell tumors likely represents the widespread application of platinum-based chemotherapy, which is particularly effective against germ cell tumors [33].

RISK FACTORS

The etiology of malignant germ cell tumors is poorly understood. Cryptorchidism is the only confirmed risk factor for testicular germ cell tumors (see Table X.5 for references). Although rare, testicular cancer coincidence in father and son, and in male siblings has been reported, implying a genetic contribution in the disease origination. Suggested risk factors for malignant germ cell tumors, mainly based on findings from studies of testicular cancer among adult populations, include maternal exogenous hormone use and high endogenous hormone level during pregnancy, pre-term birth, high birth weight, hernia, trauma, pre-natal X-ray exposure, virus infection, parental occupation and occupational exposures, and certain constitutional chromosome abnormalities.

SUMMARY

The ICCC Diagnostic Group X for GCTOG tumors represents less than 4% of tumors among children younger than 15 years of age. However, for the 15-19 year age group, these tumors account for a much higher proportion (approximately 16%) of cancer cases. The age-incidence pattern for the group of GCTOG tumors is characterized by relatively high rates in the first year of life, followed by much lower rates until puberty, when incidence begins to increase and reaches rates greater than those in the first year of life. For males, the majority of testicular cancers occurring before age 15 years are diagnosed in the first 4 years of life. However, because the incidence of testicular germ cell tumors increases rapidly after age 15, the vast majority of testicular cancer cases among those younger than 20 years of age develop among 15-19 year olds. Black males have a much lower incidence of testicular germ cell tumors than white males, while black females and white females have similar rates for ovarian germ cell tumors.

The distinctive nature of the germ cell tumors of infants and young children compared to those of adolescents and young adults complicates analyses of trends in incidence for the children younger than 20 years of age. However, over the past 20 years there has been a small absolute increase in incidence for germ cell tumors for children younger than age 15 years, with most of the increase due to higher rates for extragonadal germ cell tumors. Among children younger than 20 years of age, the incidence of GCTOG tumors has increased. The increase has been primarily driven by higher rates for gonadal germ cell tumors among 15-19 year olds and by higher rates for gonadal carcinomas among 15-19 year old females. The latter increase is attributable to changes in reporting of ovarian tumors during this time period, specifically inclusion of borderline tumors of the ovary. The increases in gonadal germ cell tumors for adolescents 15-19 years of age mirrors that observed for young adults with germ cell tumors. The onset of higher rates in males and females at the time of puberty as well as results from epidemiological studies suggest a contributory role

for hormonal influences, although the nature of these influences remains to be elucidated.

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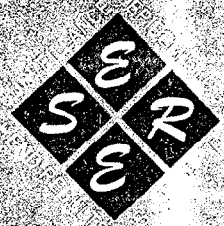
SEER PEDIATRIC MONOGRAPH



Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995

NATIONAL CANCER INSTITUTE

This publication was prepared by:

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Citation for a chapter should also include the chapter authors and chapter title.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

3048 '00 APR 24 A10 :31

Faulding Pharmaceutical Co.
Attention: Mr. Kala Patel
11 Commerce Drive
Cranford, NJ 07016

APR 18 2000

Docket No. 99P-2252/CP1

Dear Mr. Patel:

This is in response to your petition filed on July 9, 1999. We also refer to our letter dated October 22, 1999, which requested additional information, your meeting request dated November 4, 1999, and your amendments dated November 16, 1999, and January 14, 2000. You are requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug products: Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials (total drug content 30 mg), 6 mg/mL, 10 mL vials (total drug content 60 mg) and 9 mg/mL, 10 mL vials (total drug content 90 mg). The listed drug products to which you refer in your petition are Aredia® (Pamidronate Disodium for Injection) 30mg/vial, 60mg/vial, and 90 mg/vial manufactured by Novartis.

Your request involves a change in dosage form from that of the listed drug products (i.e., from a (dry solid) for injection to a (ready-to-use) injection). The change you request is the type of change that is authorized under the Act.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug products.

This petition was evaluated with respect to the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, published in the Federal Register (Pediatric Rule)(63 FR 66632) and with respect to the requirements of Section 505(j)(2)(C) of the Act. The Agency has determined that your proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement under 21 C.F.R. § 314.55(c)(2)(ii) is appropriate. The Agency has concluded that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population since the necessary studies are impossible or highly impractical because the number of such patients is small and geographically dispersed. In addition, the Agency has determined that investigations are not necessary to show safety and efficacy in the adult population.

Under the Pediatric Rule, "each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration" must contain "data that are

99P-2252

PAV1

adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective." 21 C.F.R. § 314.55(a). The Agency may waive the study requirements for some or all pediatric age groups if it concludes that:

(1) (a) The product does not represent a meaningful therapeutic benefit[1] over existing treatments, and (b) the product was not likely to be used in a substantial number of pediatric patients (21 C.F.R. § 314.55(c)(2)(i)); or

(2) the necessary studies are impossible or highly impractical, because, for example, the number of such patients is so small or geographically dispersed (21 C.F.R. § 314.55(c)(2)(ii)); or

(3) there is evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations (21 C.F.R. § 314.55(c)(2)(iii)).

The waiver request you submitted dated January 12, 2000, argued that:

(1) The change in dosage form from pamidronate disodium lyophilized powder to a ready to use solution of pamidronate disodium does not reflect a change at the point of administration and therefore is not a change in dosage form that triggers the Pediatric Rule under 21 C.F.R. § 314.55(a). You contended that the proposed change will not increase the product's use in the pediatric population but merely provides a convenience to the pharmacist/hospital.

(2) The proposed change does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients.

(3) Pamidronate disodium is indicated for use in patients with Paget's Disease and in hypercalcemia of malignancy. These diseases are primarily diseases of the adult population and have a sufficiently low prevalence that identifying adequate numbers of pediatric patients to enroll in a clinical study would present a significant challenge. Therefore, necessary studies are impossible or highly impractical because the number of patients is small and geographically diverse.

The Agency's response to your waiver request follows:

(1) The Agency considers a [Drug] for injection, and a [Drug] injection as different dosage forms; and these dosage forms are listed in separate monographs (e.g., Doxorubicin Hydrochloride Injection and Doxorubicin Hydrochloride for Injection)

---

[1] A product is considered to offer a meaningful therapeutic benefit if FDA estimates that "if approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of disease, compared to marketed products adequately labeled for that use in the relevant pediatric population" or if the drug "is in a class of drugs or for an indication for which there is a need for additional therapeutic options." 21 C.F.R. § 314.55(c)(5).

in the United States Pharmacopoeia (USP) (Please refer to General Chapter <1> in the USP). Because you are requesting a change to a new dosage form, you are subject to the Pediatric Rule under 21 C.F.R. § 314.55(a).

(2) You do not qualify for waiver under 21 C.F.R. § 314.55(c)(2)(i) because both prongs of that subparagraph must be met for you to qualify for waiver and you have not shown that your therapy, if approved, will not "represent a meaningful therapeutic benefit over existing therapies."

(3) You have met the requirement for waiver under 21 C.F.R. § 314.55(c)(2)(ii) since you have shown that necessary studies are impossible or highly impractical because the number of such patients is so small or geographically dispersed.

On the basis of this showing, under 21 C.F.R. § 314.55(c)(2)(ii) a full waiver of the requirement for pediatric studies is granted.

Under Section 505(j)(2)(C)(i) of the Act, the Agency must approve a suitability petition seeking a dosage form which differs from the dosage form of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form.

As noted above, the Agency has waived the requirement for pediatric studies under the waiver provisions of the Pediatric Rule. Moreover, the Agency finds that the change in dosage form for the specific proposed drug products do not pose questions of safety or effectiveness in the adult population because the uses, dose, and route of administration of the proposed drug products are the same as those of the listed drug products. The Agency concludes, therefore, that investigations are not necessary in this instance and that approval of your suitability petition is therefore appropriate. If shown to meet bioavailability requirements, the proposed drug products can be expected to have the same therapeutic effects as the listed reference drug products.

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the Agency has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

For your information, the listed drug products to which you refer are covered by a period of patent protection and exclusivity which appear in the Approved Drug Products With Therapeutic Equivalence Evaluations, 19th Edition, published by the Agency. The existence of such a patent protection and exclusivity will require a patent certification and an exclusivity statement upon submission of an ANDA for your proposed drug products and may also affect the approval date of any ANDA.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug products will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of

the Act. We suggest that you submit your protocol to the Office of Generic Drugs, Division of Biocquivalence for these drug products prior to the submission of your ANDA. During the review of your application, the Agency may require the submission of additional information.

The listed drug products to which you refer in your ANDA must be the ones upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Faulding Pharmaceutical, Inc.
11 Commerce Drive
Cranford, 07016New Jersey 07202

5283 '00 FEB -1 P2:23

Fax Cover Sheet

DATE: **January 14, 2000** TIME: **1:18 PM**

TO: Greg Davis, Docket Management Branch
Department of Health and Human Services
Rockville, MD
PHONE: 301 827-8762
FAX: 301 594-1174

FROM: Heike Maaser, PhD
Faudling Pharmaceuticals Co.
11 Commerce Drive, Cranford, NJ USA
PHONE: 908 931-3805
FAX: 908 704-4150

RE: **Amendment to Citizen Suitability Petition Docket No. 99P- 2252/CP1**

Number of pages including cover sheet: [3]

Message

Dear Mr. Devis,

Attached please find a copy of the Amendment to our Suitability Petition Docket No. 99P-2252/CP1, submitted to the Dockets Management Branch on January 12, 2000.

On the advise of Gordon Johnston, our Consultant, I am forwarding this amendment via fax to you to assure that our long oustanding approval will be discussed at the February 5th meeting.

Faulding appreciates your consideration,

Regards,

H. Maaser

Heike Maaser, Director, Regulatory Affairs

99P-2252

SUP 2

Faulding
A World of Health

Faulding Pharmaceutical Co
A subsidiary of Faulding Inc.
11 Commerce Drive
Cranford, New Jersey 07016
Telephone (908) 709 1200
Facsimile (908) 709 4150

AMENDMENT TO CITIZEN PETITION

5284 '00 FEB -1 P2:23

January 12, 2000

Dockets Management Branch
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

Re: Amendment to Docket No. 99P-2252/CP1
Suitability Petition – Pamidronate Disodium Injection
3 mg/mL, 6 mg/mL, 9 mg/mL

Dear Madam/Sir:

Faulding Pharmaceutical Company has been advised that it must address the Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients before final action will be taken on the above referenced suitability petition. While in disagreement with FDA's new policy involving pediatric labeling as applied to the approvability of Suitability Petitions for abbreviated new drug applications, Faulding Pharmaceutical is nevertheless submitting information in support of a waiver for pediatric studies to their Suitability Petition Docket No. 99P-2252/CP1. In accord with 21 CFR 314.55(c) FDA may grant full or partial waiver of the study requirements on its own initiative or at the request of the applicant. Faulding Pharmaceutical Company hereby requests a waiver for the following reasons:

1. The product, Pamidronate Disodium Injection (3mg/mL, 6 mg/mL, and 9 mg/mL) does not truly reflect a change in dosage form at point of administration of the drug product to the patient and will, therefore, not change/increase in any meaningful way the use of this product in the pediatric patient population. The change from a lyophilized powder to a solution provides a convenience to the pharmacist/hospital only.

2. Faulding also evaluated the prevalence of the two disease states, Paget's disease and hypercalcemia in malignancy, in the pediatric population (children from birth to 16 years of age) by conducting an exhaustive search of the available literature in the United States. Based on this research, it does not appear that the prevalence of either disease state meets the general guide for a "substantial number" of pediatric patients which the Final Rule defines as 50,000 pediatric patients.

3. The results of this search indicated that the pediatric prevalence of either Paget's disease of bone or hypercalcemia of malignancy, despite substantial variation in epidemiological data, is sufficiently low that identifying adequate patients to enroll in a clinical study would present a significant challenge. To identify patients and implement a proper study could potentially take several years due to the apparent low incidence of these disease states. Therefore, evaluation of the literature indicates that necessary studies are impossible or highly impractical because the number of patients is small and would also be geographically dispersed.

We believe that information provided in this amendment satisfies all apparent outstanding issues related to this petition. We are confident that approval of our petition will now move forward speedily especially since the agency itself communicated to Faulding Pharmaceutical Co. already on December 6, 1999 that pediatric studies would not be required.

Sincerely,
Faulding Pharmaceutical Co.

H. Maaser

Heike Maaser, Ph.D.
Director, Regulatory Affairs

NDC 0015-3215-30

PARAPLATIN®

(carboplatin for injection)

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Princeton, New Jersey 08543
USA

Each vial contains 150 mg carboplatin and 150 mg mannitol.

CONTAINS NO PRESERVATIVES
RECONSTITUTE IMMEDIATELY PRIOR TO USE

READ ACCOMPANYING CIRCULAR FOR COMPLETE DIRECTIONS FOR USE.

Store dry powder at controlled room temperature (15°-30° C) 59°-86° F. Protect from light. Reconstituted product is stable at 25° C for 8 hours.

321430DRL-3

NDC 0015-3213-30

PARAPLATIN®

(carboplatin for injection)

For I.V. Use

SINGLE-DOSE VIAL

50 mg per vial

Rx only

Lot 0B18820

Exp. Date JAN 2003

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
USA

Each vial contains 50 mg carboplatin and 50 mg mannitol.

CONTAINS NO PRESERVATIVES
RECONSTITUTE IMMEDIATELY PRIOR TO USE

READ ACCOMPANYING CIRCULAR FOR COMPLETE DIRECTIONS FOR USE.

Store dry powder at controlled room temperature (15°-30° C) 59°-86° F. Protect from light. Reconstituted product is stable at 25° C for 8 hours.

321330DRL-1

PARAPLATIN®
(carboplatin for injection)
50 mg per vial

JAN 2003
08188C

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

NDC 0015-3213-30

PARAPLATIN®
(carboplatin for injection)
For I.V. Use
SINGLE-DOSE VIAL

50 mg per vial

See top flap for lot number and expiration date.

321330DC-4

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

NDC 0015-3213-30

PARAPLATIN®
(carboplatin for injection)
For I.V. Use
SINGLE-DOSE VIAL

50 mg per vial

Rx only

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
USA

N 3 0015-3213-30 3

Each vial contains 50 mg carboplatin and 50 mg mannitol.

CONTAINS NO PRESERVATIVES
RECONSTITUTE IMMEDIATELY PRIOR TO USE

READ ACCOMPANYING CIRCULAR FOR COMPLETE DIRECTIONS FOR USE.

Store dry powder at controlled room temperature (15°-30° C) 59°-86° F. Protect from light. Reconstituted product is stable at 25° C for 8 hours.

• 1 2 3 1 2 3 1 2 3
• 1 2 3 1 2 3 1 2 3
• 1 2 3 1 2 3 1 2 3

PARAPLATIN®
(carboplatin for injection)
150 mg per vial

JAN 2003

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

NDC 0015-3214-30

PARAPLATIN®
(carboplatin for injection)

For I.V. Use

SINGLE-DOSE VIAL

See top flap or side panel for lot number and expiration date.

150 mg per vial

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS

NDC 0015-3214-30

PARAPLATIN®
(carboplatin for injection)

For I.V. Use

SINGLE-DOSE VIAL

150 mg per vial

Each vial contains 150 mg carboplatin and 150 mg mannitol.

CONTAINS NO PRESERVATIVES
RECONSTITUTE IMMEDIATELY PRIOR TO USE

READ ACCOMPANYING CIRCULAR FOR COMPLETE DIRECTIONS FOR USE.

Store dry powder at controlled room temperature (15°-30° C) 59°-86° F. Protect from light. Reconstituted product is stable at 25° C for 8 hours.

Rx only

BRISTOL LABORATORIES®
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
USA

321430DC-4

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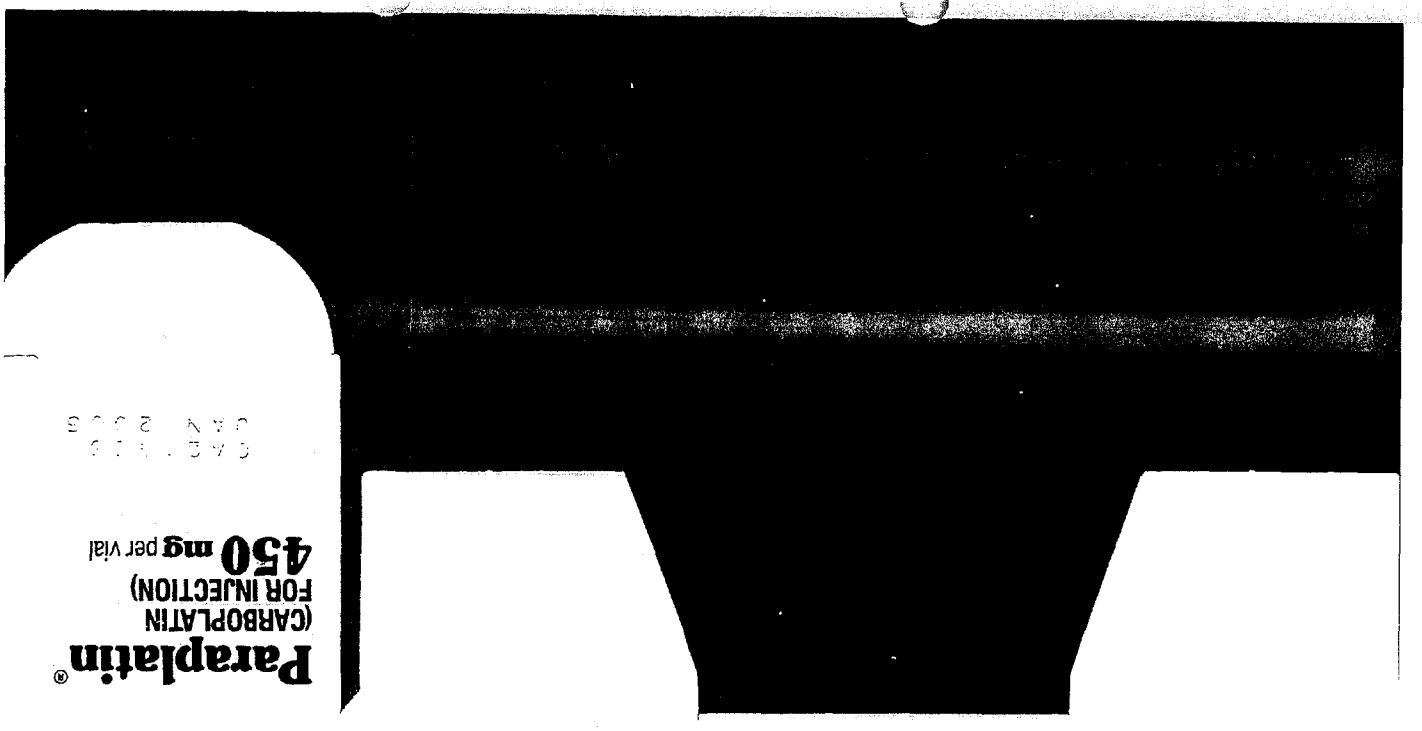


Paraplatin®
(CARBOPLATIN
FOR INJECTION)
450 mg per vial

BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

NDC 0015-3215-30
NSN 6505-01-308-2301

Paraplatin®
(CARBOPLATIN FOR INJECTION)
For I.V. Use

SINGLE-DOSE VIAL

See top flap or side panel for lot number and expiration date.

BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

NDC 0015-3215-30
NSN 6505-01-308-2301

Paraplatin®
(CARBOPLATIN FOR INJECTION)
For I.V. Use

SINGLE-DOSE VIAL

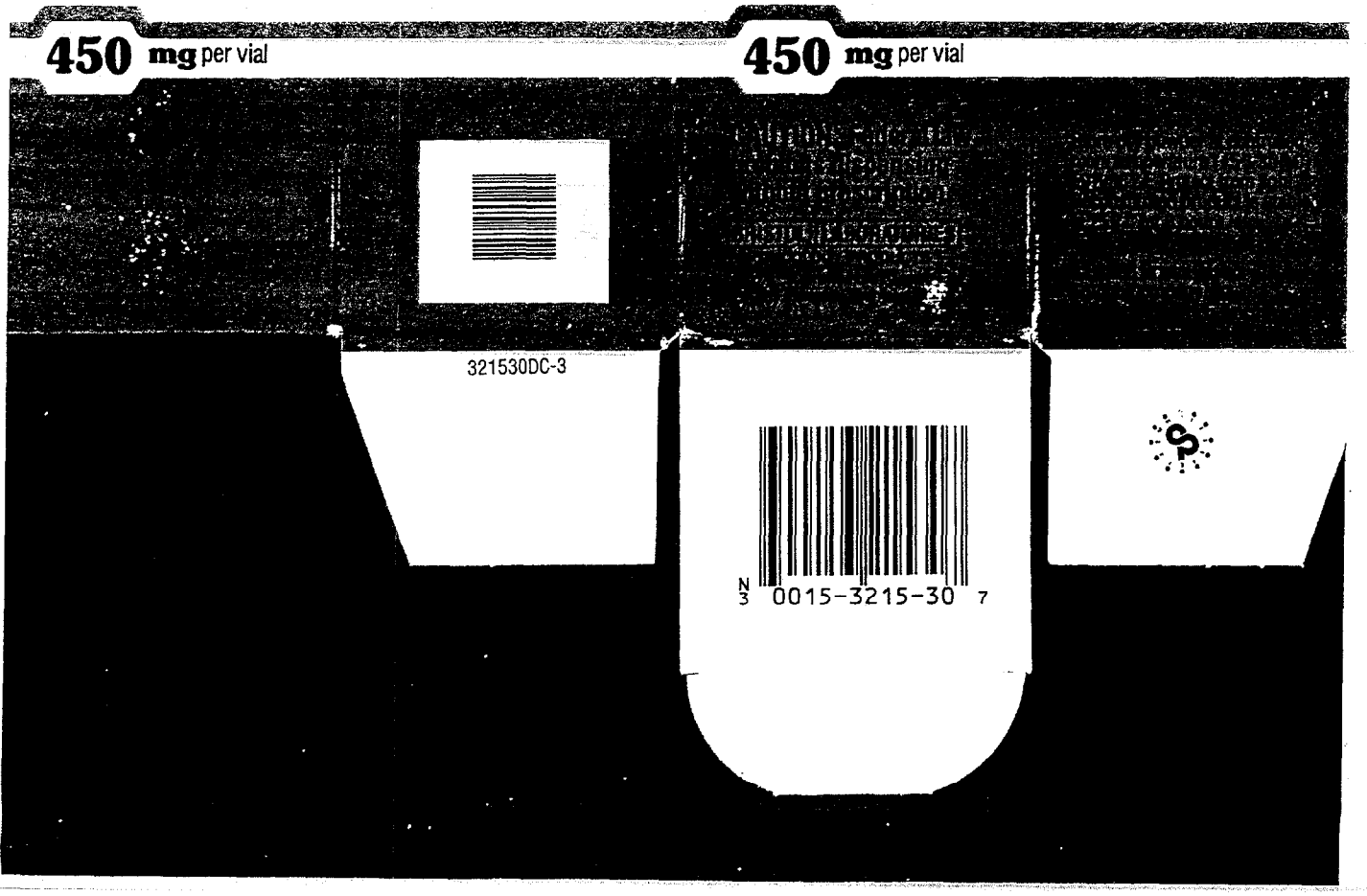
Each vial contains 450 mg carboplatin and 450 mg mannitol.

CONTAINS NO PRESERVATIVES
RECONSTITUTE IMMEDIATELY PRIOR TO USE

READ ACCOMPANYING CIRCULAR FOR COMPLETE DIRECTIONS FOR USE.

450 mg per vial

450 mg per vial



321530DC-3

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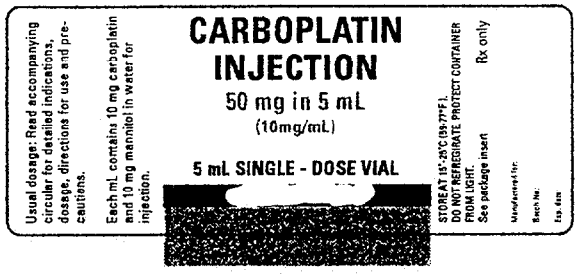
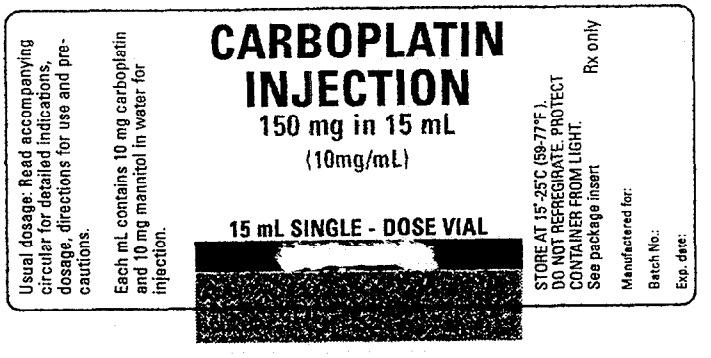
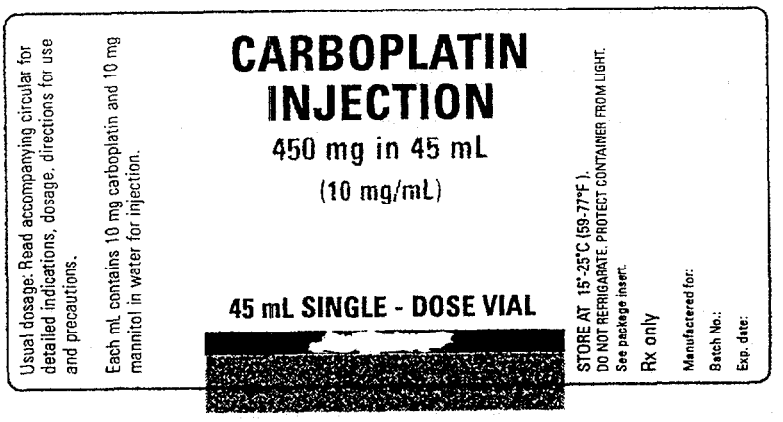

Usual dosage: Read accompanying circular for detailed indications, dosage, directions for use and precautions.
Each mL contains 10 mg carboplatin and 10 mg mannitol in water for injection.
CARBOPLATIN INJECTION
50 mg in 5 mL
(10mg/mL)
5 mL SINGLE - DOSE VIAL
STORE AT 15°-25°C (59-77°F).
DO NOT REFRIGERATE. PROTECT CONTAINER FROM LIGHT.
See package insert
Rx only

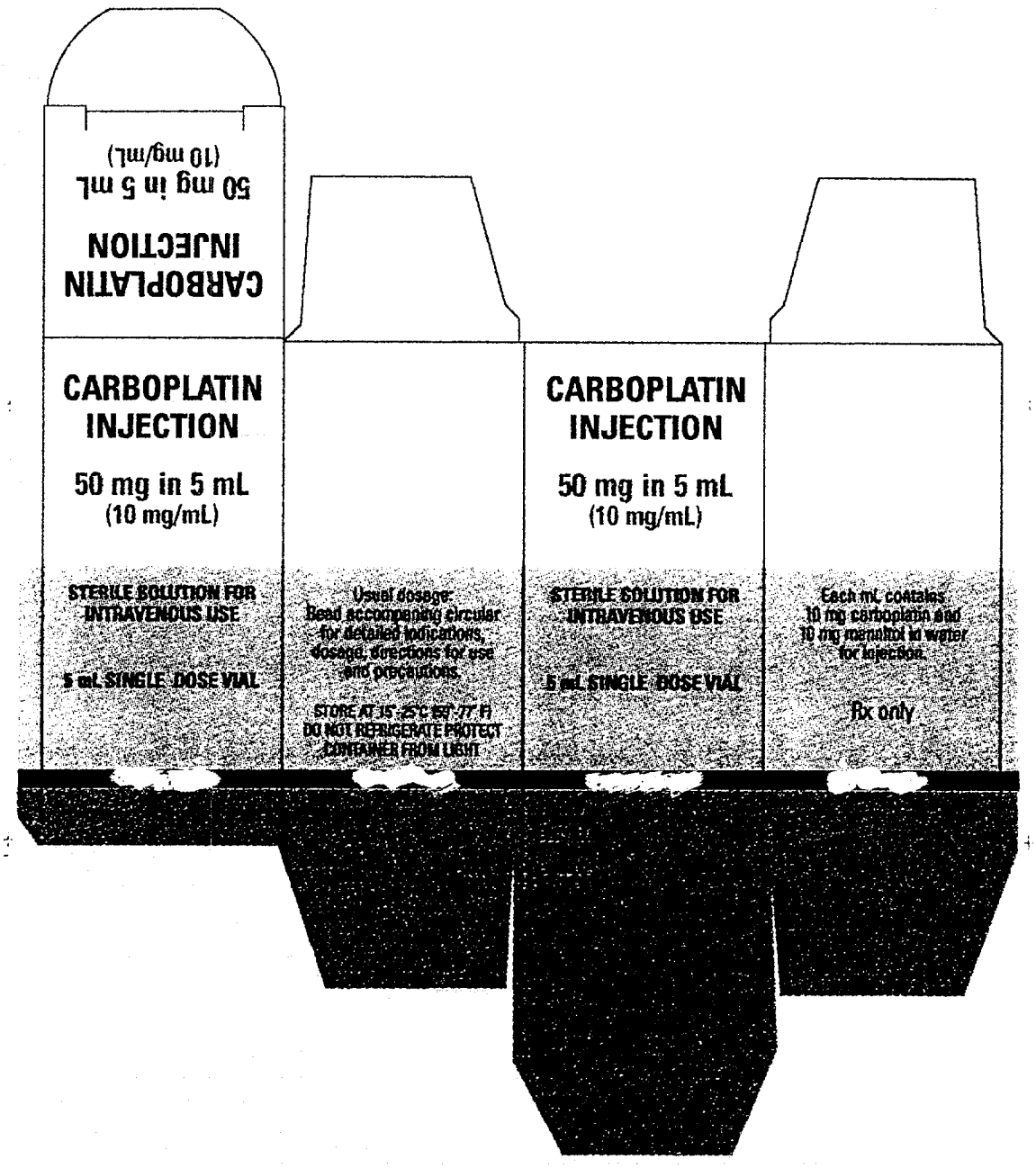
MOCK UP


Usual dosage: Read accompanying circular for detailed indications, dosage, directions for use and precautions.
Each mL contains 10 mg carboplatin and 10 mg mannitol in water for injection.
CARBOPLATIN
INJECTION
150 mg in 15 mL
(10mg/mL)
15 mL SINGLE - DOSE VIAL
STORE AT 15°-25°C (59-77°F).
DO NOT REFRIGERATE. PROTECT
CONTAINER FROM LIGHT.
See package insert
Rx only
Manufactured for:
Batch No.:
Exp. date:

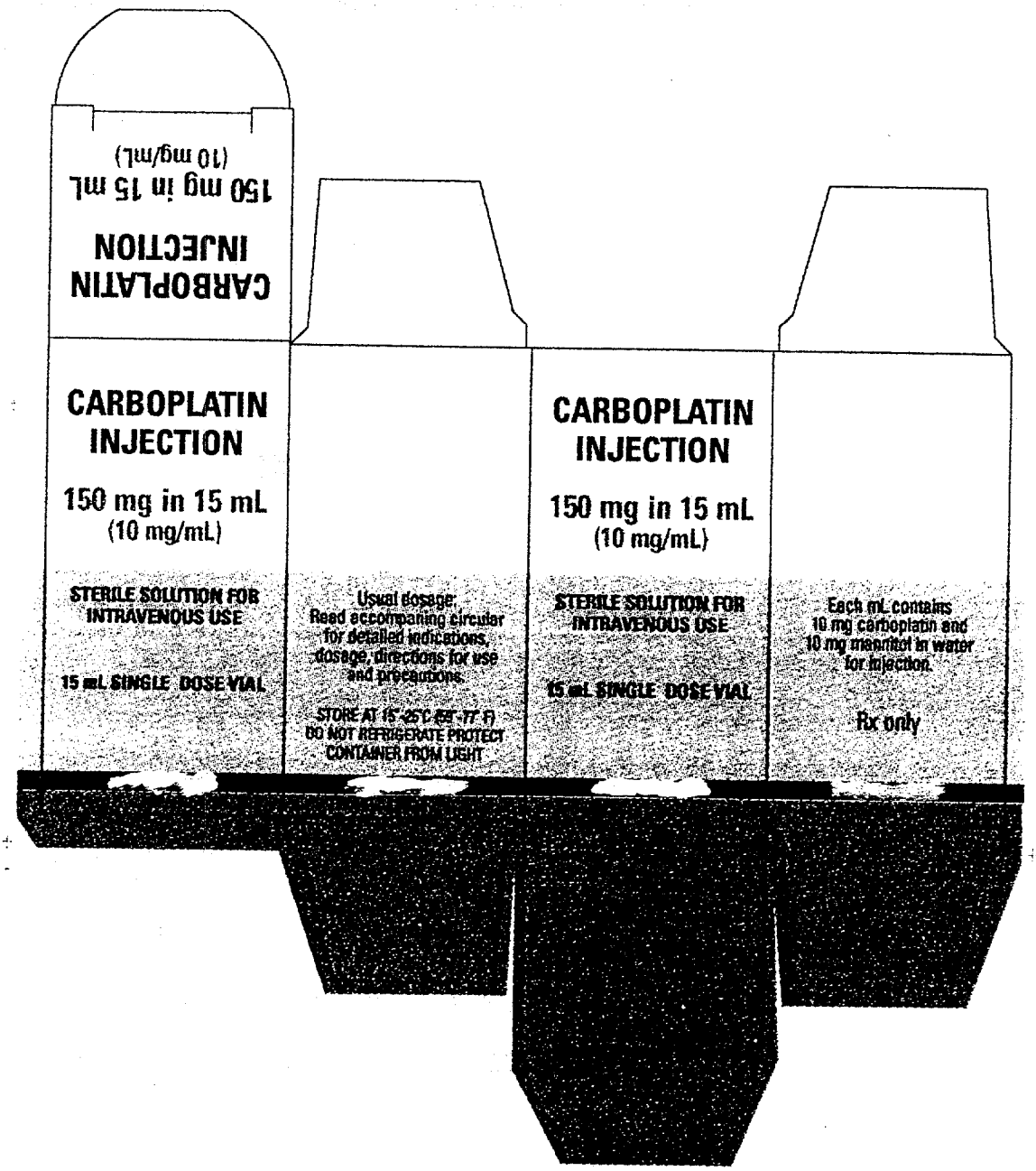
MOCK UP


Usual dosage: Read accompanying circular for detailed indications, dosage, directions for use and precautions.
Each mL contains 10 mg carboplatin and 10 mg mannitol in water for injection.
CARBOPLATIN INJECTION
450 mg in 45 mL
(10 mg/mL)
45 mL SINGLE - DOSE VIAL
STORE AT 15°-25°C (59-77°F).
DO NOT REFRIGERATE. PROTECT CONTAINER FROM LIGHT.
See package insert.
Rx only
Manufactured for:
Batch No.:
Exp. date:

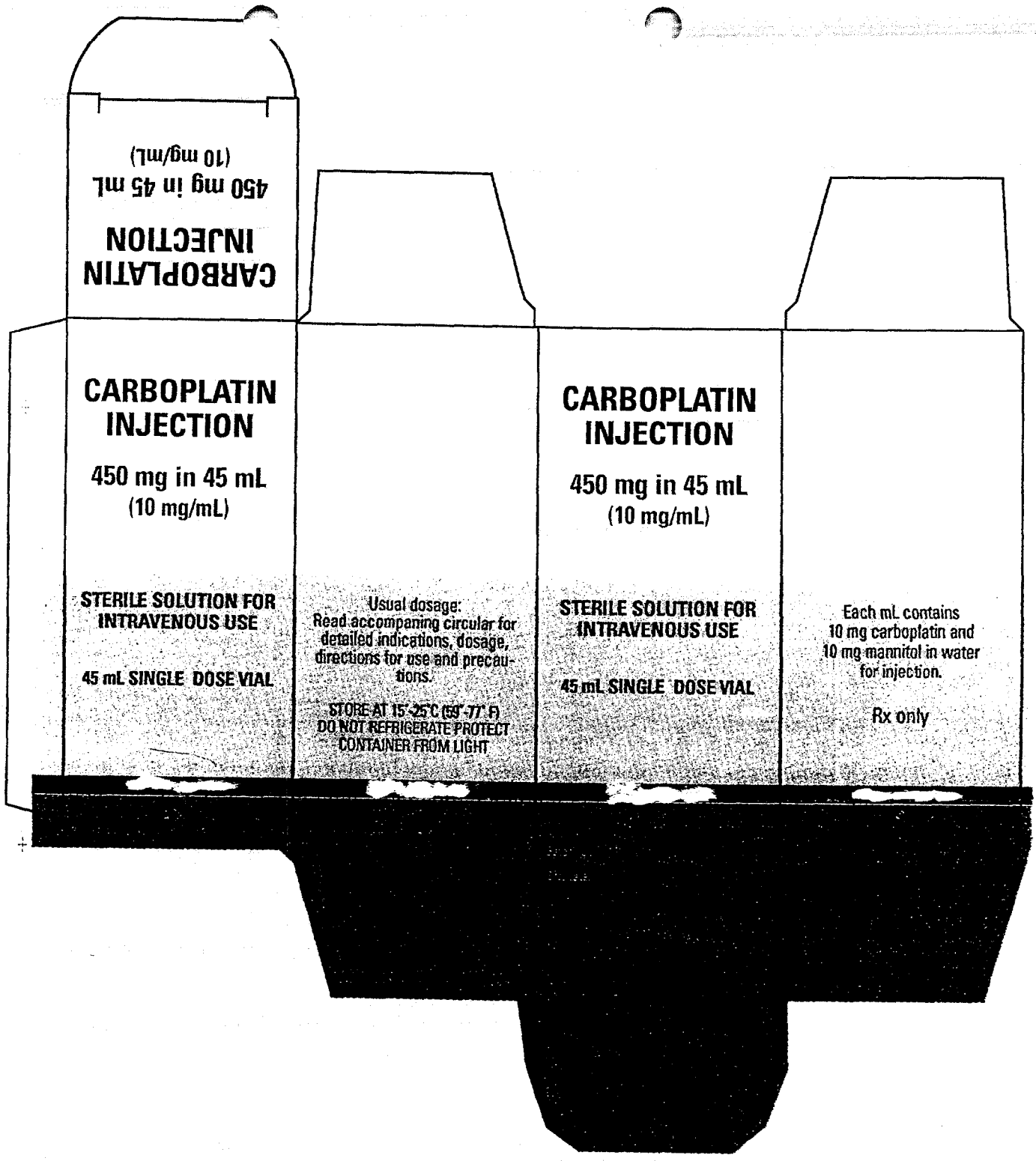
MOCK UP


CARBOPLATIN
INJECTION
50 mg in 5 mL
(10 mg/mL)
CARBOPLATIN
INJECTION
50 mg in 5 mL
(10 mg/mL)
STERILE SOLUTION FOR
INTRAVENOUS USE
5 mL SINGLE DOSE VIAL
Usual dosage:
Read accompanying circular
for detailed indications,
dosage, directions for use
and precautions.
STORE AT 15-25°C (59°-77°F)
DO NOT REFRIGERATE. PROTECT
CONTAINER FROM LIGHT
STERILE SOLUTION FOR
INTRAVENOUS USE
5 mL SINGLE DOSE VIAL
Each mL contains:
10 mg carboplatin and
10 mg mannitol in water
for injection.
℞ only

MOCK UP


CARBOPLATIN
INJECTION
150 mg in 15 mL
(10 mg/mL)
CARBOPLATIN
INJECTION
150 mg in 15 mL
(10 mg/mL)
STERILE SOLUTION FOR
INTRAVENOUS USE
15 mL SINGLE DOSE VIAL
Usual dosage:
Read accompanying circular
for detailed indications,
dosage, directions for use
and precautions.
STORE AT 15°-25°C (59°-77°F)
DO NOT REFRIGERATE PROTECT
CONTAINER FROM LIGHT
CARBOPLATIN
INJECTION
150 mg in 15 mL
(10 mg/mL)
STERILE SOLUTION FOR
INTRAVENOUS USE
15 mL SINGLE DOSE VIAL
Each mL contains
10 mg carboplatin and
10 mg mannitol in water
for injection.
Rx only

MOCK UP


CARBOPLATIN
INJECTION
450 mg in 45 mL
(10 mg/mL)
CARBOPLATIN
INJECTION
450 mg in 45 mL
(10 mg/mL)
STERILE SOLUTION FOR
INTRAVENOUS USE
45 mL SINGLE DOSE VIAL
Usual dosage:
Read accompanying circular for
detailed indications, dosage,
directions for use and precau-
tions.
STORE AT 15°-25°C (59°-77° F)
DO NOT REFRIGERATE PROTECT
CONTAINER FROM LIGHT
STERILE SOLUTION FOR
INTRAVENOUS USE
45 mL SINGLE DOSE VIAL
Each mL contains
10 mg carboplatin and
10 mg mannitol in water
for injection.
Rx only

MOCK UP