

## Correspondence

Ovarian Cancer, Oral Contraceptives, and *BRCA* Mutations

*To the Editor:* Modan and colleagues (July 26 issue)<sup>1</sup> conclude that oral contraceptives do not protect against ovarian cancer in Israeli Jewish women carrying *BRCA* mutations. We have shown, in two studies of Jewish and non-Jewish women with *BRCA* mutations, that the use of oral contraceptives was strongly protective against ovarian cancer.<sup>2,3</sup> In our recent study, the odds ratio for ovarian cancer among women who had used oral contraceptives was 0.44 (95 percent confidence interval, 0.28 to 0.68).<sup>3</sup>

Relevant differences may exist between Jews and non-Jews, between carriers of the three founder mutations common among Jews and carriers of other predisposing mutations, or between North Americans and Israelis (including the types of contraceptive pills used). To resolve the discrepancy in results between our studies and that of Modan et al., we report the results of a new case-control study of 186 women with ovarian cancer and 186 individually matched controls, all of whom were Ashkenazi Jews with *BRCA* mutations. These subjects were drawn from a registry of families with cancer and from a study of patients with cancer who were not selected on the basis of family history.<sup>4</sup> Patients had invasive ovarian cancer; controls did not, and they had both ovaries intact. Patients and controls were matched for year of birth (within one year), mutation (*BRCA1* vs. *BRCA2*), and place of residence (Israel or North America). There were 150 pairs with *BRCA1* mutations (185delAG or 5382insC), and 36 pairs with *BRCA2* mutations (6174delT); 151 pairs were from North America, and 35 were from Israel. Information on oral-contraceptive use was obtained as previously described.<sup>2,3</sup>

The odds ratio for ovarian cancer among women who had used oral contraceptives was 0.54 (95 percent confidence interval, 0.35 to 0.84;  $P=0.005$ ); the mean duration of use in this group was 4.8 years for controls and 4.3 years for pa-

tients. This corresponds to a reduction in risk of 4.4 percent for each year of use ( $P=0.056$ ). Six percent of Israeli patients and 23 percent of Israeli controls used oral contraceptives for five years or more, as compared with 18 percent of North American patients and 25 percent of North American controls. The odds ratio for ovarian cancer in the group that had used oral contraceptives for five or more years was 0.45 among North American women (95 percent confidence interval, 0.23 to 0.87) and 0.14 among Israeli women (95 percent confidence interval, 0.02 to 1.25).

Important differences between the two studies include the source of patients (we used both those drawn from a cancer registry and those not selected with respect to family history) and controls (all of our controls were mutation carriers, as compared with 1.7 percent of those in the study by Modan et al.). Nevertheless, we believe that the main reason for the discrepant results is that the controls in the study by Modan et al. were not comparable to the subgroup of patients with *BRCA* mutations. The controls were matched to all the patients with invasive ovarian cancer, but patients carrying *BRCA1* mutations are, on average, 7 to 10 years younger at the time of the diagnosis of ovarian cancer than women with sporadic cases.<sup>5</sup> Thus, the controls were born appreciably earlier than the patients with *BRCA* mutations, and in that older generation, fewer women had had long-term exposure to oral contraceptives. In fact, in the study by Modan et al., only 8.5 percent of the Israeli controls had used oral contraceptives for five or more years, as compared with 23 percent in our study. Modan et al. attempted to adjust for the difference in the year of birth by including age (in decades) in the logistic-regression analysis, but we believe that this adjustment was inadequate. Our controls were matched for age within one year. We believe that oral contraceptives are effective in reducing the risk of ovarian cancer in women with *BRCA* mutations, including Jewish women.

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## INSTRUCTIONS FOR LETTERS TO THE EDITOR

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1. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2001;345:235-40.
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*To the Editor:* Modan et al. show how genetic testing can be used to provide clear health directives under defined circumstances. Ashkenazi Jewish women with a founder mutation in their *BRCA1* or *BRCA2* gene should now be told that multiparity has a protective effect against ovarian cancer but that the use of oral contraceptives does not. However, there are currently 864 known mutations, polymorphisms, or variants of *BRCA1* alone. What should women who have one of these forms be told?

At least one founder mutation (185delAG) probably results in a *BRCA1* protein with no activity. Other, non-founder mutations presumably code for a protein with some residual function. Because cancer is a multistep process, mutations in other genes besides *BRCA1* must be involved. In fact, some *BRCA1* mutations damage the body's ability to repair DNA and thereby facilitate mutations in these other genes. Thus, the use of oral contraceptives may well protect women with some non-founder mutations. All these points may help explain the discrepancies in the literature regarding factors that confer protection against ovarian cancer.

In the future it will be helpful for a clinician to know whether a woman has a *BRCA* mutation that results in residual function, destabilizes other genes, or requires the presence of specific mutations and whether the mutation is one of a group with similar functional consequences. The clinician can use this information to determine which studies are likely to be relevant and to assess risks more accurately. We still have a great distance to go before we arrive at the best way to deal with a *BRCA*-mutation carrier in the clinic, but the work of Modan et al. shows us the way.

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The authors reply:

*To the Editor:* As Friedenson notes, ideally, clinical advice should be individualized to reflect a patient's mutation. But even with the relatively high prevalence of founder mutations among Israeli Jews, the number of women with each specific mutation is too small to allow a separate assessment of the effect of reproductive factors that has any degree of precision. A better understanding of the functional consequences of these rare mutations is probably required before we will be able to provide tailored clinical advice.

As Narod et al. note, in our case-control study involving the total population of Israeli Jews, our finding of an absence of evidence that the use of oral contraceptives pro-

TECTS AGAINST ovarian cancer among women with *BRCA1* and *BRCA2* mutations differs from the findings of their clinic-based study. They speculate that the reason for the discrepancy is that the disease is diagnosed at a much younger age in women who have a mutation than in women who do not have a mutation, and consequently, few carriers in our study had a long duration of oral-contraceptive use. In fact, the average age at diagnosis was less than three years younger in carriers than in noncarriers. Adjustment for age in pentads instead of decades made only a trivial difference in our findings; the reduction in risk for each five years of use changed from 1.0 percent (95 percent confidence interval, -23 to 27 percent) to 3.5 percent (95 percent confidence interval, -25 to 24 percent).

The pattern observed in Israeli carriers is most appropriately compared with the pattern observed in Israeli noncarriers. In particular, our results concerning the use of oral contraceptives and parity in noncarriers are strikingly similar to those of other case-control studies of ovarian cancer, even though the average duration of use is shorter in Israel than in other populations. Indeed, a test of interaction showed that the reduction in the risk of ovarian cancer conferred by the use of oral contraceptives was significantly less in carriers than in noncarriers.

Both our study and that of Narod et al. have limitations, but the proposal of Narod et al. that age differences are the source of the discrepancy in results does not appear to be correct. Methodologic differences in the identification of patients and the selection of controls or differences in the timing and level of oral-contraceptive use among women seen at clinics for high-risk women may explain the discrepant results. We regard the population-based framework of our study as a strength. Probably, as we wrote, only "additional research can resolve the discrepancy."

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## Autoimmune Diseases

*To the Editor:* The review of autoimmunity by Davidson and Diamond (Aug. 2 issue)<sup>1</sup> leaves many points open for debate. The field has never properly come to grips with the question of whether antibodies can damage or impair intact cells by binding to antigens within their cytoplasm. The Ro antigen is cytoplasmic. Is it really proved that antibodies to Ro "bind to the conducting system in the . . . heart, causing complete heart block"?

Without any qualifying remarks, the statement that "cardiac ischemia and necrosis cause heart-specific autoreactivity and myocarditis" is misleading. Dressler's syndrome is an uncommon complication of myocardial infarction. The vast majority of cases of myocardial infarction do not result in autoimmunity, nor do burns, severe tissue trauma, or most infections, unless the host has a particular set of suscepti-

bility genes, which are present in only a small number of persons. Susceptibility genes must also be present in animal models in which tissue damage leads to autoimmunity.

The "danger hypothesis" has been oversold. On the one hand, massive tissue damage and infection do not generally trigger autoimmunity. On the other hand, the repeated intravenous administration of pure, deaggregated, endotoxin-free mouse antibodies almost inevitably provokes the formation of antimouse antibodies. If it did not do so, we would be using mouse monoclonal antibodies as therapeutic agents much more often than we do. Self-tolerance is alive and well.

Finally, the authors state that "the incidence of disease declines as the distance from regions where the disease is endemic increases." Surely this is a truism. How could it be otherwise?

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The authors reply:

*To the Editor:* Dr. Goding's chief point seems to be that there are many areas of ignorance and controversy regarding autoimmune diseases. With this, we certainly agree. As for the particular issues he raises: first, anti-Ro antibodies have been shown to destroy the atrioventricular node in the fetal, not the maternal, heart; they have not been shown to bind directly to the conducting system. Second, we hope we did not imply that all tissue injury leads to autoimmunity and autoimmune disease. We cited an animal study in which T cells from animals subjected to myocardial ischemia were adoptively transferred into a normal animal and caused myocarditis. This example served to demonstrate that autoreactivity can arise in the absence of foreign antigen. We hope we have stated clearly that autoimmunity and autoimmune disease, whatever the trigger, arise only in a susceptible host.

It is clear that there are many ways to induce autoimmunity; one of them is through the presence of a proinflammatory microenvironment. We are not aware that we advanced the so-called danger hypothesis as a unifying theory of autoimmunity. This hypothesis will become useful when we know the molecular identity of the danger signal, the receptor or receptors to which it binds, and the ways in which cell function is then altered. At that point, we will have a mechanistic explanation. At this point, there is still much to be learned about autoimmunity.

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### The Coxibs, Selective Inhibitors of Cyclooxygenase-2

*To the Editor:* The review article by FitzGerald and Patrono (Aug. 9 issue)<sup>1</sup> on the coxibs, selective inhibitors of

cyclooxygenase-2 (COX-2), included a table listing pharmacokinetic and metabolic features as well as drug interactions. According to the table, in patients taking warfarin, rofecoxib causes a 10 percent increase in the international normalized ratio (INR), but there is no interaction between celecoxib and warfarin.

Since the introduction of celecoxib in Australia in October 1999, the Adverse Drug Reactions Advisory Committee has received 2218 reports of suspected adverse drug reactions. Of these, 21 involved an increase in INR values in patients treated with celecoxib and warfarin, some of whom had large hemorrhages.<sup>2</sup> In addition to these cases, there were 11 cases of bleeding in patients who took both drugs but for whom INR values are not given. In these patients, the bleeding may have been the result of a drug interaction, an additive effect of the two drugs, or an effect of celecoxib alone, or it may have been unrelated to the celecoxib therapy.

Since warfarin is metabolized mainly by cytochrome CYP2C9 and since this enzyme can be inhibited by celecoxib, some patients may have substantial inhibition of CYP2C9, resulting in higher plasma concentrations of warfarin. Two recent reports described this interaction,<sup>3,4</sup> but no comprehensive evaluation of either celecoxib or rofecoxib has been performed. The reports of adverse reactions should prompt precisely that type of study.

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1. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med* 2001;345:433-42.
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3. Mersfelder TL, Stewart LR. Warfarin and celecoxib interaction. *Ann Pharmacother* 2000;34:325-7.
4. Haase KK, Rojas-Fernandez CH, Lane L, Frank DA. Potential interaction between celecoxib and warfarin. *Ann Pharmacother* 2000;34:666-7.

*To the Editor:* FitzGerald and Patrono failed to address the renal toxicity of the COX-2-inhibitor drugs. Although preliminary data suggested that these drugs might have less nephrotoxicity than the nonselective nonsteroidal antiinflammatory drugs,<sup>1</sup> emerging data suggest that the COX-2 inhibitors have substantial nephrotoxicity. The risk of nephrotoxic effects appears to be particularly high in patients with decreased renal perfusion (for example, those with volume depletion or congestive heart failure), in whom prostaglandins play a critical part in maintaining renal blood flow.

Perazella and Eras recently described three cases of reversible acute renal failure in patients taking a selective COX-2 inhibitor.<sup>2</sup> In these patients, acute renal failure was reversed by the cessation of COX-2-inhibitor therapy, although one patient required hemodialysis. In another report, the occurrence of acute tubulointerstitial nephritis and acute renal failure due to rofecoxib was described.<sup>3</sup> This is hardly surprising, considering that COX-2 is constitutively expressed in glomeruli, the renal interstitium, and the renal vasculature. Because of this emerging risk profile, it seems prudent to avoid the use of these drugs in patients with compromised renal blood flow.<sup>4</sup>

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1. Whelton A, Maurath CJ, Verburg KM, Geis GS. Renal safety and tolerability of celecoxib, a novel cyclooxygenase-2 inhibitor. *Am J Ther* 2000;7:159-75. [Erratum, *Am J Ther* 2000;7:341.]
2. Perazella MA, Eras J. Are selective COX-2 inhibitors nephrotoxic? *Am J Kidney Dis* 2000;35:937-40.
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*To the Editor:* I disagree with the recommendation of FitzGerald and Patrono that low-dose aspirin be given to mitigate the potential prothrombotic effects of COX-2 inhibitors. The theoretical basis for a prothrombotic effect of these drugs is their ability to alter the metabolism of arachidonic acid to favor thromboxane formation over prostaglandin formation.<sup>1</sup> This effect is opposite to that of aspirin. The use of a nonselective, and irreversible, cyclooxygenase inhibitor such as aspirin is likely to negate any potential gastrointestinal benefit of a COX-2 inhibitor. This conclusion is supported by the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, in which rofecoxib was not associated with fewer gastrointestinal side effects than naproxen in patients taking aspirin.<sup>2</sup> The only way to avoid the potential adverse cardiovascular effects of COX-2 inhibitors is to avoid their use in patients with risk factors for cardiovascular disease.

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1. Crofford LJ, Oates JC, McCune WJ, et al. Thrombosis in patients with connective tissue diseases treated with specific cyclooxygenase 2 inhibitors: a report of four cases. *Arthritis Rheum* 2000;43:1891-6.
2. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.

The authors reply:

*To the Editor:* Drug interactions emerge initially as case reports, such as those alluded to by the correspondents, and such anecdotal observations may prompt rational study. Thus, despite initial evidence suggesting the absence of an interaction between warfarin and celecoxib, we agree with Dr. Killen that further evaluation of this possibility is now appropriate. Similarly, we agree with Dr. Nzerue's advocacy of further evaluation of the renal effects of coxibs.

In response to Dr. Rich: the effect of low-dose aspirin on the risk-benefit ratio of coxibs can be assessed only in controlled clinical trials. As discussed in our review, it remains unknown whether coxibs represent a cardiovascular hazard and, if so, in which patients. Although we have raised the possibility of such a hazard,<sup>1,2</sup> the results of the VIGOR study with respect to cardiovascular effects may be explicable in terms of chance or the effects of naproxen, as mentioned in our review.

A report that followed the publication of our review<sup>3</sup> claimed that both celecoxib and rofecoxib increase the risk of cardiovascular events, a claim that attracted considerable media attention. Although one might expect a prostacyclin-based mechanism to be a class effect, we question the statistical approach used in that study and thus the validity

of the conclusions. For now, studies that further explore the cardiovascular pharmacology of the coxibs are necessary to determine which, if any, patients are at risk for cardiovascular events from these drugs.

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1. McAdam BE, Catella-Lawson F, Mardini IA, Kapoor S, Lawson JA, FitzGerald GA. Systemic biosynthesis of prostacyclin by cyclooxygenase (COX)-2: the human pharmacology of a selective inhibitor of COX-2. *Proc Natl Acad Sci U S A* 1999;96:272-7. [Erratum, *Proc Natl Acad Sci U S A* 1999;96:5890.]
2. Catella-Lawson F, McAdam B, Morrison BW, et al. Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. *J Pharmacol Exp Ther* 1999;289:735-41.
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## Medical Mystery — The Answer

The medical mystery in the October 18 issue<sup>1</sup> involved a 78-year-old woman with hypertension and diabetes who was hospitalized with cellulitis of her left lower leg. Colicky right-flank pain associated with nausea and vomiting developed. Intravenous urography showed no evidence of calculi or ureteral obstruction. However, a lithopedion in the right lower quadrant of the abdomen was noted (Fig. 1). The



Figure 1. A Lithopedion.

woman said she had had three pregnancies, all of which had resulted in term deliveries. Her menses had ceased at approximately 45 years of age. She had no history of abnormal vaginal bleeding, amenorrhea, or abdominal pain.

Lithopedion is derived from the Greek words *lithos*, meaning stone, and *paidion*, meaning child. It describes an extrauterine fetus that has become calcified. This rare event, estimated to occur in 1 of every 700,000 pregnancies, requires the presence of a medically undetected extrauterine pregnancy with continued asepsis of the products of conception. A fetus that dies within the first three months of pregnancy will be absorbed; survival of the fetus for more than three months results in a nidus for calcification and lithopedion formation.

Our patient's symptoms resolved spontaneously. Although a fetus retained in the abdomen can be removed surgically, the patient's age and coexisting conditions precluded such an operation.

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*Editor's note:* We received 736 responses to this medical mystery. About 72 percent of the respondents said that the abdominal radiograph showed a dead or retained fetus; 196 said it showed a lithopedion or "stone baby," 174 an ectopic or extrauterine pregnancy, 117 a calcified or mummified fetus, 30 a dead fetus, and 10 a retained fetus. Another 18 said the radiograph showed a fetus papyraceus, which is a fetus that has died in utero and been pressed flat against the uterine wall by the growth of a living twin. Other responses included teratoma (44), cecal volvulus (19), current pregnancy (17), dermoid cyst (15), and dentures (11).

### Web Sites and Misinformation about Illicit Drugs

*To the Editor:* The letter by Boyer et al. (Aug. 9 issue)<sup>1</sup> decrying the prevalence of "partisan" sites on illicit-drug use neglected to mention that theoretically objective government sites contain misinformation about drugs as well. For example, the National Institute on Drug Abuse publication "Marijuana: Facts for Teens"<sup>2</sup> says that marijuana users are 104 times more likely to use cocaine than those who do not use marijuana and that because "marijuana use can affect thinking and judgment, users can forget to have safe sex and possibly expose themselves to HIV [human immunodeficiency virus], the virus that causes AIDS."

With this kind of fear-mongering and exaggeration (which is hardly nonpartisan), it is not surprising that teenagers look to alternative sources for their information about drugs. And since government sites explicitly refuse to provide information that could help teenagers reduce the risks related to drug use, there is a vacuum that alternative sites seek to fill.

What is needed is genuinely objective information — neither the government's fear-mongering nor the downplay-

ing of risks seen on some of the alternative sites. In the context of a so-called war on drugs, however, no one should be shocked that official sites are dismissed as propaganda. That's why the Office of National Drug Control Policy calls its Web site for teenagers Freevibe.com and hides the fact that it runs the site — anything called ".gov" would not be credible.

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1. Boyer EW, Shannon M, Hibberd PL. Web sites with misinformation about illicit drugs. *N Engl J Med* 2001;345:469-71.
2. National Institute on Drug Abuse. Marijuana: facts for teens (revised). Bethesda, Md.: National Institutes of Health, 1998. (NIH publication no. 98-4037)

The authors reply:

*To the Editor:* We appreciate the comments of Ms. Szalavitz, but we believe that her observations are erroneous. For example, she suggests that illicit substances have minimal effect on sexual behavior. Several studies performed in the United States and Europe, however, find that drug use increases the risk of sexually transmitted diseases and HIV infection.<sup>1,2</sup> Szalavitz's argument that scientifically derived data become less credible if they are cited on a U.S. government Web site lacks merit. We would suggest that this information is presented not with fear-mongering in mind, but in order to give an honest and accurate description of the risks associated with illicit-drug use.

In our opinion, teenagers do not turn to partisan Web sites because they object to the content of government sites; adolescents visit such sites because they want to learn about drugs. The point of our report was that those interested in learning about drugs of abuse will easily find partisan information promoting the use of these drugs, whereas antidrug Web sites require greater effort to locate.

Szalavitz proposes the creation of Web sites that contain objective information in an attempt to reduce the risks of illicit-drug use. That sounds reasonable. Unfortunately, "harm reduction" is often a euphemism for the legalization of substances of abuse.<sup>3</sup> The use of these substances was criminalized because they were harmful; they are not harmful because they were criminalized. If their illegal status represents a bias, then at least it is a bias toward healthful and safe living.

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## Nephrectomy and Interleukin-2 for Metastatic Renal-Cell Carcinoma

*To the Editor:* In this issue of the *Journal*, Flanigan et al.<sup>1</sup> report the results of a randomized trial conducted by the Southwest Oncology Group (SWOG), which compared interferon alone with nephrectomy followed by interferon for the treatment of metastatic renal-cell cancer. There was a survival advantage in the surgery-plus-interferon group, as well as in all the risk strata. Similar results have been demonstrated in Europe by the Genito-Urinary Group of the European Organisation for Research and Treatment of Cancer, in a study with a similar protocol.<sup>2</sup> However, the issue of the most effective immunotherapeutic agent to use after nephrectomy is still unsettled because no prospective trials have addressed this question. We used our program's Kidney Cancer Database, containing the records of more than 450 patients with metastatic renal-cell cancer who have received immunotherapy, to obtain survival data on patients treated with interleukin-2 after undergoing nephrectomy.

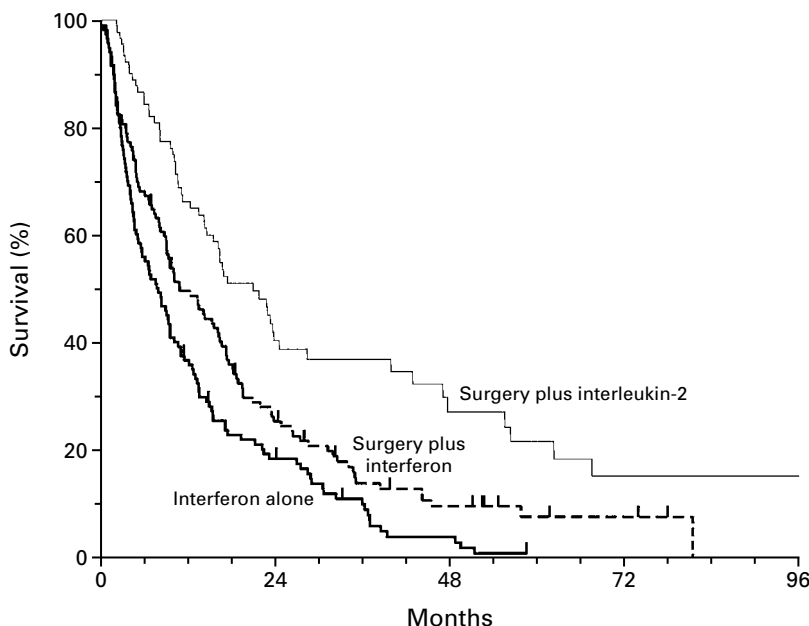
We identified 89 patients who met the eligibility criteria for the SWOG study and who had been treated with interleukin-2-based regimens after undergoing nephrectomy. The survival of these patients, analyzed with the use of the Kaplan–Meier method, was compared with the survival of 120 patients in the SWOG surgery-plus-interferon group (Fig. 1). The median survival of the patients treated with nephrectomy plus interleukin-2 was 16.7 months — twice the survival in the SWOG interferon-only group and 5 months longer than that in the SWOG surgery-plus-interferon group

( $P < 0.05$  with the use of the reported 95 percent confidence interval of 9.2 to 16.5 months for the SWOG surgery-plus-interferon group). The rate of survival at five years was 19.6 percent in the group of patients who received interleukin-2, as compared with 10 percent in the group of patients who received interferon. The median survival in a group of contemporaneous, eligible patients undergoing nephrectomy alone at the University of California, Los Angeles (UCLA), was 7.2 months, which was not significantly different from the median survival in the SWOG interferon-only group (8.1 months; 95 percent confidence interval, 5.4 to 9.5) or from the median survival at 6 months in a group of historical UCLA controls who received no treatment at all.<sup>3</sup>

Our analysis suggests that the survival of patients with metastatic renal-cell cancer can be improved by treatment with nephrectomy followed by adjuvant immunotherapy. Either nephrectomy or immunotherapy alone appears to be of less benefit. Although our data are retrospective, we believe that they support the use of interleukin-2 after nephrectomy in patients with metastatic renal-cell cancer. The data warrant validation in a randomized trial comparing the two cytokines.

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**Figure 1.** Kaplan–Meier Analysis of Survival among Patients with Metastatic Renal-Cell Carcinoma Who Were Treated with Nephrectomy plus Interleukin-2, Nephrectomy plus Interferon, or Interferon Alone.

The median survival was 16.7 months for the patients who received interleukin-2 after nephrectomy and 11.1 months for those who received interferon after nephrectomy ( $P < 0.05$ ).

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