REPORTS

Multiple Primary Cancers in Families With Li–Fraumeni Syndrome

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Background: **Li–Fraumeni syndrome is a dominantly inherited disorder characterized by early-onset breast cancer, sarcomas, and other cancers in children and young adults. Members of families with this syndrome also develop multiple primary cancers, but the frequency is unknown. To approach this issue, we quantified the incidence of second and third primary cancers in individuals from 24 Li–Fraumeni kindreds originally diagnosed with cancer during the period from 1968 through 1986.** ***Methods:*** **The relative risk (RR) of subsequent cancers and 95% confidence intervals (CIs) were calculated by use of population-based incidence data from the Connecticut Cancer Registry. Kaplan–Meier analysis was used to determine the cumulative probability (± standard error) of subsequent cancers.** ***Results:*** **Among 200 Li–Fraumeni syndrome family members diagnosed with cancer, 30 (15%) developed a second cancer. Eight individuals (4%) had a third cancer, while four (2%) eventually developed a fourth cancer. Overall, the RR of occurrence of a second cancer was 5.3 (95% CI = 2.8–7.8), with a cumulative probability of second cancer occurrence of 57% (±10%) at 30 years after diagnosis of a first cancer. RRs of second cancers occurring in families with this syndrome were 83.0 (95% CI = 36.9–187.6), 9.7 (95% CI = 4.9–19.2), and 1.5 (95% CI = 0.5–4.2) for individuals with a first cancer at ages 0–19 years, 20–44 years, and 45 years or more, respectively. Thirty (71%) of 42 subsequent cancers in this group were component cancers of Li–Fraumeni syndrome.** ***Conclusions:*** **Compared with the general population, members of Li–Fraumeni syndrome families have an exceptionally high risk of developing multiple primary cancers. The excess risk of additional primary cancers is mainly for cancers that are characteristic of Li–Fraumeni syndrome, with the highest risk observed for survivors of childhood cancers. Cancer survivors in these families should be closely monitored for early manifestations of new cancers. [J Natl Cancer Inst 1998;90:606–11]**

Li–Fraumeni syndrome (LFS), an autosomal-dominant disorder, features the occurrence of breast cancer in young women and of soft tissue sarcomas, osteosarcomas, brain tumors, acute leukemias, and adrenocortical tumors in children and young adults *(1–7).* Germline mutations in the p53 tumor suppressor gene (also known as TP53) have been identified in approximately one half of LFS families in the literature *(8–12).* Our follow-up studies of LFS families revealed that new cancers, including multiple primary cancers, continued to develop among at-risk relatives *(13).* The current study quantifies the frequency of multiple primary cancers in these kindreds.

Subjects and Methods

Study Population

Study subjects are members of 24 LFS kindreds who were enrolled in the Cancer Family Registry in the Division of Cancer Epidemiology and Genetics, National Cancer Institute, during the period from 1968 through 1986 *(1,2).* Initial informed consent of some families utilized standard procedures that antedated institutional review boards, whereas subsequent studies were performed with written consent on protocols approved by the institutional review board of the Dana-Farber Cancer Institute. We recontacted family members to identify cancers, births, and deaths that occurred after the last systematic follow-up in 1986. A total of 1004 blood relatives in the affected lineages were enumerated for this study.

Diagnoses of cancer were based on available medical records, pathology reports, and death certificates. Written consent to review medical records was obtained from living subjects or next of kin of decedents. The diagnosis of multiple primary cancers was based on findings of malignant neoplasms of different histologic types or primary anatomic sites. Multiple primary breast cancers were diagnosed when these cancers differed in histology or occurred more than 5 years apart without metastases to other sites. Unconfirmed cancers, carcinomas of the skin, and *in situ* carcinomas were excluded from analysis. The majority of unconfirmed cancers were diagnosed before 1985. Available specimens from affected members of 16 of the 24 families were analyzed for germline p53 mutations. Eight (50%) of these 16 kindreds had germline p53 mutations *(8,9).* No blood specimens were available from affected members of the remaining eight families because of cancer mortality.

Treatment records of patients with multiple cancers were reviewed for information regarding types of treatment (surgery, chemotherapy, and radiation therapy), specific chemotherapeutic agents and doses used, and radiation fields and doses. Treatment data were unavailable for patients whose cancer diagnosis was based on death certificates or pathology reports only.

Statistical Methods

Analyses were performed on all family members with confirmed cancers and on subgroups on the basis of age at diagnosis and type of first cancer. Person-years of observation for second cancers extended from the date of first cancer diagnosis to the date of second cancer diagnosis, death, loss to follow-up, or close of the study in October 1995. Observed numbers of cancers were compared with expected numbers estimated by multiplying appropriate person-years at risk by age-, sex-, and calendar

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See ''Notes'' following ''References.''

year-specific incidence rates for all primary cancers in the state of Connecticut (i.e., on the basis of data from the Connecticut Cancer Registry) *(14–16)*. Relative risks (RRs) of second cancers were the ratios of observed versus expected numbers of cancers, assuming a Poisson distribution for the number of second cancers in the LFS cohort. The Dean Score test was used to test for Poisson overdispersion of the age-specific counts stratified by 5-year calendar periods *(17)*. The asymptotic 95% confidence intervals (CIs) were computed, adjusting for overdispersion as measured by Pearson's χ^2 statistics *(18)*. The cumulative probability of second cancers and the standard errors (SEs) were estimated by Kaplan–Meier analysis and Greenwood's formula *(19)*. Differences in the cumulative probability of cancer on the basis of age at first cancer diagnosis and cancer type were evaluated by Mantel–Haenszel logrank tests *(20)*. The cumulative probability of third cancers occurring among those with double primary cancers was determined in the same manner.

The possibility of selective ascertainment of families with individuals who had multiple cancers prompted a subset analysis of living subjects who did not have second cancers at initial ascertainment. The period of observation for second cancers in these patients started from the date of family ascertainment for case subjects previously diagnosed with cancer and the date of first cancer diagnosis for those who had been cancer free. Criteria for withdrawal from observation were unchanged. Of 85 case subjects excluded from the subgroup analysis, 77 died and eight had developed multiple primary cancers before the ascertainment date.

Results

Two hundred cancer patients (96 males and 104 females) in the 24 families were eligible for study (Table 1). These 200 patients accumulated 1142 person-years of follow-up before diagnosis of second primary cancer (30 patients), death (120 patients), loss to follow-up (two patients), or study closure (48 patients). The first cancers in 140 individuals (70%) were diagnosed before age 45 years, including 62 diagnosed within the first two decades of life. There were 140 cancers (70%) that were characteristic of LFS, i.e., breast cancers (45 women), soft tissue sarcomas (34 patients), osteosarcomas (25 patients), brain tumors (20 patients), leukemias (11 patients), and adrenocortical carcinomas (five patients). In later life, family members tended to develop cancers of the lung (13 patients), colon (seven patients), and pancreas (seven patients), as well as malignant lymphomas (seven patients).

The 30 individuals from the LFS families with a second cancer occurrence developed a total of 72 primary cancers (Table 2). The intervals between diagnosis of the first and second primary cancers ranged from 1 to 27 years (median, 6 years). Eight patients had a third cancer, and four of them eventually developed a fourth cancer. The neoplasms featured in LFS accounted for 54 (75%) of these 72 cancers, including 24 breast cancers and 22 sarcomas.

Kaplan–Meier analysis showed a cumulative second cancer probability of 57% (±10% [±SE]) at 30 years of follow-up (Fig. 1, A). The cumulative probability was higher among 34 patients who initially had soft tissue sarcomas, i.e., 64% (±16%) at 20 years and 100% at 30 years of follow-up. On the basis of the 30 patients with a second primary cancer, the cumulative probability of a third cancer was 38% (±12%) at 10 years after the diagnosis of a second cancer (Fig. 1, B).

Subgroup analysis of the 115 cancer survivors (56 males and 59 females) who were free of a second cancer at initial ascertainment showed that 23 subsequently developed second cancers. Their cumulative probability of developing second cancers was 54% (±11%) at 25 years of follow-up, which is comparable to the estimate for the entire series.

The age-adjusted incidence rate of second cancer in the 24 LFS families (2.6 per 100 person-years) exceeded the expected cancer rate for the general population (RR = 5.3; 95% CI = 2.8–7.8) (Table 3). The rate was highest among those with cancer initially diagnosed before 20 years of age (3.2 per 100 person-years) and declined with age. Consequently, RRs of second cancer differed markedly by age at first cancer diagnosis (Table 3). Patients with the cancers featured in LFS did not have a higher incidence of second cancers when compared with the incidence among those with other cancers (data not shown). Patients in families with a germline p53 mutation did not have a higher incidence of second cancers when compared with the incidence among those in families without a known p53 mutation (data not shown).

Treatment records for 27 of the 30 patients who had multiple primary cancers showed that nine had received radiotherapy for their first cancer (five also had chemotherapy), three had chemotherapy only, and 15 had neither treatment. Most irradiated patients received megavoltage cobalt-60 × rays (range, 35–70 Gy). Six irradiated patients (Nos. 1, 4, 5, 12, 16, and 30) developed a total of eight solid tumors within the radiation field at 3–22 years after treatment for the first cancer (median, 11 years) (Table 2). In addition, the radiation field for the third cancer in one patient (No. 12) encompassed the site of her fourth cancer 7 years later. One other patient (No. 24) developed acute leukoerythroblastic leukemia 2 years after treatment for a brain tumor with carmustine and cranial irradiation, a known leukemogenic regimen *(21,22)*.

Table 1. Tumor types and ages at diagnosis of 200 first cancers in Li–Fraumeni syndrome family members*

	No. of patients with cancer (No. with second cancer) by age at first cancer diagnosis			
First cancer	0–19 y	20–44 y	⩾45 y	All ages
Cancers featured in Li–Fraumeni syndrome				
All types	55 (9)	64 (13)	21 (2)	140 (24)
Breast cancer	0 (0)	33 (9)	12 (1)	45 (10)
Soft tissue sarcoma	18 (5)	11 (3)	5 (1)	34 (9)
Osteosarcoma	17 (3)	7 (0)	1 (0)	25 (3)
Brain tumor	9 (0)	10 (1)	1 (0)	20 (1)
Leukemia	7 (1)	2 (0)	2 (0)	11 (1)
Adrenocortical carcinoma	4 (0)	1 (0)	0 (0)	5 (0)
Other cancers†	7 (1)	14 (1)	39 (4)	60 (6)
Total cancers	62 (10)	78 (14)	60 (6)	200 (30)

*Based on 200 first cancers in 24 Li–Fraumeni syndrome kindreds identified during the period from 1968 through 1986. Study subjects were enrolled in the Cancer Family Registry, Division of Cancer Epidemiology and Genetics, National Cancer Institute.

†Lung cancer (13), lymphoma (7), colon cancer (7), pancreatic cancer (7), cancer of the uterus/ovaries (6), prostate cancer (5), kidney cancer (2; renal cell carcinoma and Wilms' tumor), cancer of esophagus (2), stomach cancer (2), bladder cancer (2), and neuroblastoma, gallbladder cancer, liver cancer, thyroid cancer, laryngeal cancer, cancer of the thorax, and skin cancer (melanoma) (1 each).

Table 2. Multiple primary cancers in 30 Li–Fraumeni syndrome family members diagnosed with a second cancer

Patient No.	Sex*	Sequence of tumor types (age at diagnosis in years)†			
		First	Second	Third	Fourth
1	M	SS (1)	SS‡,§,‖ (23)		
2	F	SS (2)	Brain (6)		
3	F	SS (2)	Breast (29)		
4	M	SS (4)	OS§ (15)		
5	M	SS (12)	SS§,‖ (27)		
6	F	SS (24)	Breast (34)		
7	F	SS (28)	Breast (32)		
8	F	SS (35)	SS‖ (42)	Breast (48)	
9	M	SS (50)	Lymphoma (51)	Melanoma (53)	
10	M	OS (6)	SS‡ (17)		
11	M	OS (14)	Brain (26)		
12	F	OS (16)	SS§ (19)	Breast (29)	Breast‡,§,‖ (36)
13	F	Breast (22)	Thyroid (30)	Breast (34)‖	Ovary (50)
14	F	Breast (24)	Gastric (40)		
15	F	Breast (25)	Ovary (29)	Brain (30)	
16	F	Breast (30)	Breast‖ (36)	Mesothelioma§ (40)	SS§ (41)
17	F	Breast (32)	Breast‖ (47)		
18	F	Breast (33)	Breast‖ (35)		
19	F	Breast (33)	Breast‖ (42)		
20	F	Breast (39)	Pancreas (58)	Breast‖ (60)	
21	F	Breast (42)	Breast‖ (46)		
22	F	Breast (57)	Breast‖ (59)		
23	M	Leukemia (2)	Leukemia‡ (11)		
24	F	Brain (26)	Leukemia (28)		
25	M	Kidney (15)	SS (16)		
26	M	Lung (55)	SS (62)	Lung‡ (64)	Lymphoma (65)
27	M	Larynx (35)	Lung‡ (39)		
28	F	Ovary (68)	Leukemia (71)		
29	F	Pancreas (47)	Bladder (53)		
30	M	Prostate (62)	SS§ (66)		

*M = male; F = female.

†Cancer classification: SS = soft tissue sarcoma; OS = osteosarcoma. All others except brain tumors were carcinomas unless otherwise specified.

‡Histologically different from the previous cancer(s).

§Tumors occurred in the previous radiation field.

‖*See* text for criteria to determine multiple primary cancers.

Discussion

Members of families with inherited cancer syndromes such as LFS tend to develop multiple primary cancers at early ages *(2,23–26)*. This prospective study examined the frequency of multiple primary cancers in members of 24 LFS kindreds identified up to three decades ago. Thirty of 200 family members with cancer developed multiple primary cancers. Kaplan–Meier analysis showed a 57% cumulative probability of second cancer at 30 years after diagnosis of the first cancer. Third cancers developed at an even higher rate, although the number of patients with a third cancer was small. Most neoplasms in these families were component cancers of LFS, suggesting that inherited susceptibility was the major predisposing factor.

Cancer incidence rates are low among children in the general population and rise steadily with increasing age. In contrast, rates of second cancer in our series were highest among childhood cancer survivors, who had an 83-fold excess risk (Table 3); however, no excess risk was found in family members with first cancers after age 45 years (Table 3), suggesting that late-onset cancers among family members might be due to chance or factors other than inherited predisposition. The RRs of second cancers were similar among patients whose first cancers are typical of LFS versus those with other neoplasms. This finding raises the possibility that some of these other neoplasms are rare manifestations of LFS *(11)*.

Somatic mutations in the p53 gene are found in a high proportion of human cancers, whereas germline mutations are rare *(27,28)*. Inherited p53 gene mutations have been detected in approximately one half of LFS kindreds and rarely in young patients with multiple primary cancers *(29–34)*. Within the 24 families whom we studied, the increased incidence of second cancers was not associated with having a germline p53 gene mutation. Families with normal p53 alleles might have germline mutations in other highly penetrant genes that produce an autosomal-dominant pattern of similar cancers. These genes can be sought by linkage studies of p53-negative families and molecular analyses. Candidate germline mutations may be in genes involved in the p53 signal transduction pathway.

Ionizing radiation is a known risk factor for virtually all cancers except chronic lymphocytic leukemia *(35,36)*. Its carcinogenic effects are dose dependent, and high-dose radiotherapy can contribute to development of second cancers *(36–41)*. Sensitivity to radiation-induced cancers has been reported in clinical studies of patients with germline mutations in the p53 gene and in p53-deficient mice *(42–44)*. In our study, available data on treatment of the first cancers suggest that radiotherapy contributed to eight subsequent solid tumors in six patients and to acute leukemia in a seventh patient who also received chemotherapy. The 3- to 22-year interval between radiation treatment and solid tumor development is consistent with the latent periods for radiation carcinogenesis *(37,45)*. The latent period, which is shorter for radiation leukemogenesis, was 2 years in our patient with secondary leukemia after radiotherapy and carmustine chemotherapy. These findings parallel our observation that radiotherapy further increases the risk of second cancer among retinoblastoma patients with germline RB1gene mutations *(23)*.

Our study design may have selected for LFS families known to have multiple primary cancers. Consequently, a subset analysis was restricted to second cancers that developed after initial ascertainment of the kindreds. A similar risk estimate was found, suggesting that substantial selection bias is unlikely. Overestimation may have resulted by including 15 patients with multiple sarcomas or bilateral breast cancers. However, five of these patients had third cancers as additional manifestations of their susceptibility to multiple primary cancers. Calculation of risk of second cancer also excluded unconfirmed cancers and applied histologic, anatomic, and temporal criteria for diag-

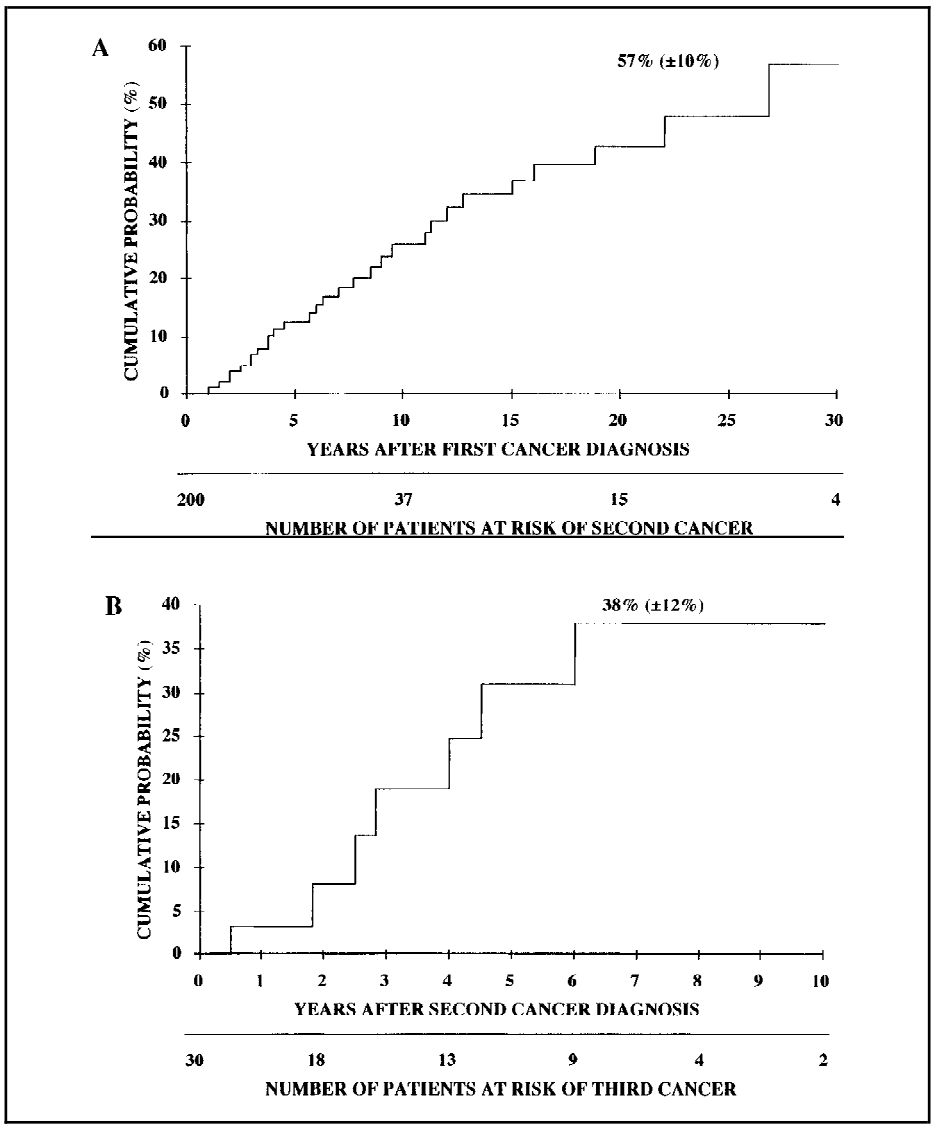

Fig. 1. A) Kaplan–Meier analysis of cumulative probability (± standard error) of second primary cancers during follow-up of 200 patients with a first cancer in families with Li–Fraumeni syndrome. The cumulative probability of a second cancer at 30 years was 57% (±10%). **B)** Kaplan–Meier analysis of cumulative probability (± standard error) of third primary cancers during follow-up of 30 patients with double primary cancers in families with Li–Fraumeni syndrome. The cumulative probability of a third cancer at 10 years was 38% (±12%).

nosis of independent primary sarcomas or breast cancers. Selective loss to follow-up is not an explanation for our findings because only two of the 200 cancer patients in the study were lost to observation. The sharp decline in RR of second cancer with age argues against a generalized risk overestimation due to greater diligence in seeking cancer in our families. Use of the population-based comparison data from the Connecticut Tumor Registry for all primary cancers is a standard approach to minimize the problem of inaccuracy of second cancer diagnosis and unstable estimates due to infrequent occurrence of second cancers in the general population *(39,41,46)*. Evidence of Poisson overdispersion (Dean Score test, one-sided $P = .03$) was taken into account by the adjustment of the 95% CIs by use of Pearson's χ^2 test statistics. This approach broadened the 95% CIs by approximately 25% compared with the 95% CIs obtained with the use of the exact method.

Table 3. Second cancers among 200 members of Li–Fraumeni syndrome families, according to age at first cancer diagnosis*

Age at first cancer diagnosis, y	No. of study subjects	Second cancer rate/100 PY (No. of cancers/PY)	RR† (95% CI)
0–19	62	3.2 (10/312)	83.0 (36.9–187.6)
20–44	78	2.7 (14/522)	9.7 (4.9–19.2)
⩾45	60	2.0 (6/308)	1.5 (0.5–4.2)
All ages	200	2.6 (30/1142)	5.3 (2.8–7.8)

*PY = person-years of observation; RR = relative risk; CI = confidence interval.

†RR was calculated by use of observed/expected number of cases: 10/0.12 for ages 0–19 years, 14/1.45 for ages 20–44 years, 6/4.08 for ages ⩾45 years, and 30/5.67 for all ages combined.

Uncertainties exist regarding strategies to reduce second cancer morbidity and mortality in LFS families *(47)*. The second cancers in these families can arise over several decades in diverse organs and anatomic sites, regardless of the first tumor type or the family's germline p53 gene status. Although the efficacy of screening for carriers of a mutated p53 gene is unknown, mammography and clinical breast examinations starting in early adulthood are consistent with current management strategies for carriers of the BRCA1 and BRCA2 mutations *(47–49)*. Prophylactic mastectomy is problematic for women who have germline p53 mutations and a predisposition for additional cancer *(50)*. Surveillance of blood cell counts to detect early leukemia can be considered, although the likelihood of finding occult leukemia is small and survival benefits are uncertain. Thus, no recommendations can be made for implementing other costly or invasive screening tests for the diverse solid tumors featured in LFS *(51)*. It is prudent to suggest that all family members pursue a healthy lifestyle and avoid environmental carcinogens and that their physicians be alert for early signs of cancer *(47)*. Emerging evidence for the efficacy of certain chemopreventive agents may prompt studies on genetically susceptible populations such as LFS families *(47,52)*. In particular, chemoprevention data on p53 knockout mice can help identify candidate agents for human studies *(53)*. However, the rarity of LFS families would necessitate a major international collaborative effort to launch a clinical trial *(50)*.

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Notes

Supported by Public Health Service grant 5RO1HG00725 from the National Center for Human Genome Research, National Institutes of Health, Department of Health and Human Services; by the Cornelius V. Starr Foundation; by the Liberty Mutual Group; and by the Boston Foundation.

We are indebted to Gene Pannello for his contribution in statistical analysis. We thank all families involved in this study.

Manuscript received July 25, 1997; revised December 10, 1997; accepted February 12, 1998.

Oral Transmucosal Fentanyl Citrate: Randomized, Double-Blinded, Placebo-Controlled Trial for Treatment of Breakthrough Pain in Cancer Patients

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Background: **Patients with cancer frequently experience episodes of acute pain, i.e., breakthrough pain, superimposed on their chronic pain. Breakthrough pain is usually treated with short-acting oral opioids, most of which provide some relief after 15–20 minutes, with peak effects after 30–45 minutes. Oral transmucosal fentanyl citrate (OTFC), a unique formulation of the opioid fentanyl, has been shown to provide meaningful pain relief within 5 minutes in patients following surgery. We conducted a multicenter, randomized, double-blinded, placebo-controlled trial of OTFC for cancer-related breakthrough pain.** ***Methods:*** **Patients who were 18 years of age or older, receiving the equivalent of at least 60 mg oral morphine or at least 50 μg transdermal fentanyl per day for chronic cancer-related pain, and experiencing at least one episode of breakthrough pain per day were studied. After titration to an effective OTFC dose, subjects were given 10 randomly ordered treatment units (seven OTFC units and three placebo units) in the form of identical lozenges. If acceptable pain relief was not achieved within 30 minutes, subjects were instructed to take their previous breakthrough pain medication (i.e., rescue medication). Pain intensity, pain relief, and use of rescue medication were evaluated at 15-minute intervals over a 60-minute period.** ***Results:*** **Eighty-nine of 92 patients who received the randomized treatment were assessable (i.e., treated with at least one unit of OTFC and one unit of placebo). OTFC produced significantly larger changes in pain intensity and better pain relief than placebo at all time points (two-sided *P*<.0001). Episodes treated with placebo required the use of rescue medication more often than episodes treated with OTFC (34% versus 15%; relative risk = 2.27; 95% confidence interval = 1.51–3.26; two-sided *P*<.0001).** ***Conclusions:*** **OTFC appears effective in the treatment of cancer-related breakthrough pain. [J Natl Cancer Inst 1998;90:611–6]**

In addition to persistent pain *(1)*, patients with cancer frequently experience superimposed intermittent episodes of acute pain, which is commonly referred to as incident or breakthrough pain *(2)*. These transient and often intense flares of pain can be a particularly troublesome feature of chronic cancer-related pain *(3)*. Although few studies *(2,4)* have been conducted to examine this problem specifically, recent reports indicate that breakthrough cancer pain, severe to excruciating in intensity, occurs in up to 65% of patients with cancer and is frequently undertreated.

The current standard of care for treating cancer pain is to provide a sustained-release preparation that controls the chronic, persistent pain and a rapid, relatively short-acting analgesic that relieves the breakthrough pain without lingering so long as to cause somnolence once the painful episode has subsided. Although data demonstrating efficacy have not been published, the mainstays of breakthrough pain therapy are short-acting oral opioids that are generally believed to have an onset of 15–20 minutes and a peak effect after 30–45 minutes.

Oral transmucosal fentanyl citrate (OTFC) is a unique formulation in which fentanyl, a potent and short-acting opioid that binds primarily to the morphine (mu)

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See ''Notes'' following ''References.''