The New England Journal of Medicine

VOLUME 344 JANUARY 11, 2001 NUMBER 2

CELLULAR-TELEPHONE USE AND BRAIN TUMORS

PETER D. INSKIP, SC.D., ROBERT E. TARONE, PH.D., ELIZABETH E. HATCH, PH.D., TIMOTHY C. WILCOSKY, PH.D., WILLIAM R. SHAPIRO, M.D., ROBERT G. SELKER, M.D., HOWARD A. FINE, M.D., PETER M. BLACK, M.D., JAY S. LOEFFLER, M.D., AND MARTHA S. LINET, M.D.

ABSTRACT

Background Concern has arisen that the use of hand-held cellular telephones might cause brain tumors. If such a risk does exist, the matter would be of considerable public health importance, given the rapid increase worldwide in the use of these devices.

Methods We examined the use of cellular telephones in a case–control study of intracranial tumors of the nervous system conducted between 1994 and 1998. We enrolled 782 patients through hospitals in Phoenix, Arizona; Boston; and Pittsburgh; 489 had histologically confirmed glioma, 197 had meningioma, and 96 had acoustic neuroma. The 799 controls were patients admitted to the same hospitals as the patients with brain tumors for a variety of nonmalignant conditions.

Results As compared with never, or very rarely, having used a cellular telephone, the relative risks associated with a cumulative use of a cellular telephone for more than 100 hours were 0.9 for glioma (95 percent confidence interval, 0.5 to 1.6), 0.7 for meningioma (95 percent confidence interval, 0.3 to 1.7), 1.4 for acoustic neuroma (95 percent confidence interval, 0.6 to 3.5), and 1.0 for all types of tumors combined (95 percent confidence interval, 0.6 to 1.5). There was no evidence that the risks were higher among persons who used cellular telephones for 60 or more minutes per day or regularly for five or more years. Tumors did not occur disproportionately often on the side of head on which the telephone was typically used.

Conclusions These data do not support the hypothesis that the recent use of hand-held cellular telephones causes brain tumors, but they are not sufficient to evaluate the risks among long-term, heavy users and for potentially long induction periods. (N Engl J Med 2001;344:79-86.)

HAND-HELD cellular telephones were introduced to the U.S. market in 1984[1] but were not widely used until the mid-1990s. By early 2000, the number of subscribers to cellular-telephone services had grown to an estimated 92 million in the United States and 500 million worldwide.[2,3] Some concern has arisen about adverse health effects, especially the possibility that the low-power microwave-frequency signal transmitted by the antennas on handsets might cause brain tumors or accelerate the growth of subclinical tumors.[4-8] It is generally agreed that the heating of brain tissue by cellular telephones is negligible, and that any carcinogenic effect would have to be mediated through a nonthermal mechanism, the nature and existence of which remain a matter of speculation.[5,7-13] Direct genotoxic effects are unlikely.[7,14-16]

Data concerning the risk of cancer associated with the exposure of humans to nonionizing radiation of the frequencies used by cellular telephones are limited,[4,6,7,17-19] and review panels have called for additional research.[5,8,20-22] We report the results of a case–control study that was initiated in 1993, shortly after the possibility of a link between use of cellular telephones and brain tumors received extensive media attention and elicited public concern.

METHODS

Study Setting and Population

The study methods have been described in detail previously.[23] The study was conducted at hospitals in Boston (Brigham and Wom-

From the Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics (P.D.I., R.E.T., E.E.H., M.S.L.), and the Neuro-Oncology Branch (H.A.F.), National Cancer Institute, Bethesda, Md.; the Epidemiology and Medical Studies Program, Research Triangle Institute, Research Triangle Park, N.C. (T.C.W.); the Department of Neurology, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Ariz. (W.R.S.); the Division of Neurosurgery, Western Pennsylvania Hospital, Pittsburgh (R.G.S.); Brigham and Women's Hospital, Boston (P.M.B.); and the Department of Radiation Oncology, Massachusetts General Hospital, Boston (J.S.L.). Address reprint requests to Dr. Inskip at Executive Plaza S., Rm. 7052, 6120 Executive Blvd., Rockville, MD 20852, or at inskippe@mail.nih.gov.

en's Hospital); Phoenix, Arizona (St. Joseph's Hospital and Medical Center); and Pittsburgh (Western Pennsylvania Hospital). Each is a regional referral center for the diagnosis and treatment of brain tumors. Institutional review boards at the National Cancer Institute and all participating hospitals approved the protocol, and written informed consent was obtained from each subject or from his or her proxy. Enrollment began in June of 1994 and ended in August of 1998. The study was restricted to adults 18 years old or older who received care at one of the participating hospitals, resided within 50 miles of the hospital (or within Arizona, in the case of the Phoenix center), and could understand English or Spanish.

Eligible patients with tumors were those in whom a first intracranial glioma or neuroepitheliomatous tumor (codes 9380 to 9473 and 9490 to 9506 of the *International Classification of Diseases for Oncology, 2nd edition* [ICD-O-2][24]), hereafter referred to as glioma, intracranial meningioma (ICD-O-2 codes 9530 to 9538), or acoustic neuroma (ICD-O-2 code 9560) had been diagnosed within the eight weeks preceding hospitalization at a participating hospital. Microscopical confirmation was required for gliomas and meningiomas, and a confirmatory magnetic resonance imaging (MRI) or computed tomographic (CT) scan was required for acoustic neuromas (96 percent of which were also confirmed microscopically). The tumor grade of gliomas was classified according to the guidelines of Kleihues et al.[25,26] The location of the tumor was determined on the basis of the MRI, CT, and surgical reports. Of the potentially eligible patients with tumors, 92 percent agreed to participate in the study. Most (80 percent) were enrolled and interviewed within three weeks after the qualifying diagnosis.

The controls were patients who were admitted to the same hospitals for a variety of nonmalignant conditions and were frequency-matched to the total group of patients with tumors according to hospital, age (in 10-year strata), sex, race or ethnic group, and proximity of their residence to the hospital (0 to 8 km, >8 to 24 km, >24 to 48 km, >48 to 80 km, or >80 km [0 to 5 mi, >5 to 15 mi, >15 to 30 mi, >30 to 50 mi, or >50 mi]). Priority for approaching candidates for the control group was determined by the relative numbers of patients with tumors and controls in the different strata. Of the eligible controls who were contacted, 799 (86 percent) participated.

Data Collection

A research nurse administered a computer-assisted, personal interview in the hospital. Proxy interviews were conducted if the subject was too ill or functionally impaired or had died. Proxy interviews were necessary for 16 percent of the patients with glioma, 8 percent of the patients with meningioma, 3 percent of the patients with acoustic neuroma, and 3 percent of the controls. The usual proxy was the spouse. Interviews were audiotaped if the respondent consented, and nearly all respondents did so.

The interview questions concerned the use of hand-held cellular telephones (with the antenna on the handset), car telephones, and transportable cellular telephones with separate battery packs.[4] Participants were asked about the calendar years of the first and last use; the duration of "regular" use (defined as at least two calls per week within this period); the usual frequency of use (in minutes per day); and the hand usually used to hold the handset. The questions concerning the duration and frequency of use were asked only of persons who reported using a particular type of telephone more than five times in their lives. A card was shown displaying photographs of different types of cellular and cordless telephones, and the interviewer's script included a description of the distinguishing features of each type. The managers of the study listened to audiotapes of this portion of the interview for all study subjects and corrected the data when any discrepancies were found.

Also covered in the interview were the subject's educational level, household income, type of health insurance coverage, religion, marital status, history of medical exposure to ionizing radiation, and handedness. The subjects' addresses were linked with 1990 U.S. Census data files to determine the median household income for the census block or tract in which the person resided at the time of hospital admission.

Statistical Analysis

Conditional logistic regression[27,28] was used to estimate odds ratios, compute confidence intervals, and perform likelihood-ratio tests (two-sided tests at an α level of 0.05). Odds ratios were used as estimates of the relative risk. In addition to the matching variables, the analyses accounted for the date of the interview (a continuous variable), the type of respondent (the subject, a proxy, or both), educational level (less than high school, high school or general equivalency diploma, one to three years of college, or four years of college or more), annual household income (six categories, from less than $15,000 to $75,000 or more), type of health coverage, marital status, religion, history of radiotherapy to the head or neck, and handedness.

The association between the laterality of the tumor and the self-reported laterality of telephone use was examined among the patients with tumors. The relative risk associated with the use of hand-held cellular telephones was estimated as $(\sqrt{OR}+1) \div 2$ (where OR denotes odds ratio), on the basis of an approach described elsewhere.* Two-sided P values for tests of independence were based on Fisher's exact test.

RESULTS

Characteristics of Patients with Tumors and Controls

The 782 patients with tumors included 489 with glioma, 197 with meningioma, and 96 with acoustic neuroma (Table 1). Nearly 71 percent of the patients with gliomas had been given a diagnosis of glioblastoma or other type of astrocytoma, and 17 percent a diagnosis of oligodendroglioma or mixed glioma (mostly oligoastrocytomas). Patients with high-grade gliomas outnumbered those with low-grade gliomas (354 vs. 135). The ratios of men to women were 1.3 among patients with glioma, 0.3 among patients with meningioma, and 0.6 among those with acoustic neuroma. The most common reasons for hospitalization among the 799 controls were injuries (197) and disorders of the circulatory (179), musculoskeletal (172), digestive (92), and nervous (58) systems. Diagnoses in the controls varied among the hospitals, with trauma accounting for the largest fraction in Phoenix (35 percent), circulatory diseases in Boston (29 percent), and musculoskeletal diseases in Pittsburgh (41 percent). The patients with tumors tended to be older than the controls, more highly educated, and from homes with higher household incomes (Table 1); these differences were most pronounced in the patients with acoustic neuromas.

Among the controls, 232 (29 percent) reported having used a hand-held cellular telephone more than five times; the proportion who reported use at that level was 29 percent among patients hospitalized with trauma, 22 percent among those with circulatory disease, 31 percent among those with musculoskeletal disorders, and 33 percent among other patients. The proportion of controls who reported having used a hand-held cellular telephone more than five times increased during the course of the study, whereas the corresponding proportions for the use of car phones and

*See http://www.nejm.org or NAPS document no. 05579 for 2 pages of supplementary material. To order the NAPS document, contact NAPS, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.

TABLE 1. SELECTED CHARACTERISTICS OF PATIENTS WITH BRAIN TUMORS AND CONTROL PATIENTS.*

CHARACTERISTIC	CONTROL PATIENTS (N=799)	PATIENTS WITH GLIOMA† (N=489)	PATIENTS WITH MENINGIOMA (N=197)	PATIENTS WITH ACOUSTIC NEUROMA (N=96)	ALL PATIENTS WITH BRAIN TUMORS (N=782)
	number of patients (percent)				
Location of hospital					
Phoenix, Ariz.	405 (51)	244 (50)	99 (50)	72 (75)	415 (53)
Boston	220 (28)	153 (31)	79 (40)	22 (23)	254 (32)
Pittsburgh	174 (22)	92 (19)	19 (10)	2 (2)	113 (14)
Age at interview‡					
18–39 yr	247 (31)	131 (27)	32 (16)	17 (18)	180 (23)
40–59 yr	314 (39)	178 (36)	88 (45)	51 (53)	317 (41)
60–90 yr	238 (30)	180 (37)	77 (39)	28 (29)	285 (36)
Sex					
Female	436 (55)	212 (43)	151 (77)	60 (63)	423 (54)
Male	363 (45)	277 (57)	46 (23)	36 (37)	359 (46)
Race or ethnic group					
Non-Hispanic white	715 (89)	444 (91)	163 (83)	89 (93)	696 (89)
Hispanic white	54 (7)	26 (5)	14 (7)	6 (6)	46 (6)
Black	19 (2)	10 (2)	9 (5)	0	19 (2)
Asian	1 (<1)	4 (1)	4 (2)	1 (1)	9 (1)
Native American	6 (1)	2 (<1)	2 (1)	0	4 (1)
Other or unknown	4 (1)	3 (1)	5 (3)	0	8 (1)
Educational level					
<High school	105 (13)	64 (13)	24 (12)	5 (5)	93 (12)
High school or GED	234 (29)	122 (25)	57 (29)	28 (29)	207 (26)
1–3 yr of college	245 (31)	130 (27)	68 (35)	21 (22)	219 (28)
4 yr of college	105 (13)	89 (18)	23 (12)	23 (24)	135 (17)
Graduate or professional school	89 (11)	68 (14)	24 (12)	18 (19)	110 (14)
Unknown	21 (3)	16 (3)	1 (1)	1 (1)	18 (2)
Self-reported annual household income					
<$15,000	125 (16)	44 (9)	16 (8)	2 (2)	62 (8)
$15,000–$24,999	115 (14)	73 (15)	32 (16)	10 (10)	115 (15)
$25,000–$34,999	105 (13)	69 (14)	30 (15)	12 (12)	111 (14)
$35,000–$49,999	134 (17)	84 (17)	31 (16)	26 (27)	141 (18)
$50,000–$74,999	145 (18)	79 (16)	32 (16)	16 (17)	127 (16)
≥$75,000	124 (16)	102 (21)	39 (20)	25 (26)	166 (21)
Unknown	51 (6)	38 (8)	17 (9)	5 (5)	60 (8)

*The location of the hospital, the age at the time of the interview, the sex, and the race or ethnic group were matching variables. GED denotes general equivalency diploma.

†The glioma category includes neuroepitheliomatous tumors (ICD-O-2 codes 9380 to 9473 and 9490 to 9506[24]). There were 236 glioblastomas, 5 gliosarcomas, 70 anaplastic astrocytomas, 34 other or unspecified astrocytomas, 46 oligodendrogliomas, 9 anaplastic oligodendrogliomas, 30 mixed gliomas, 7 ependymomas, 3 anaplastic ependymomas, 3 subependymal gliomas, 18 gangliogliomas, 4 neurocytomas, 5 medulloblastomas, 1 primitive neuroectodermal tumor, 2 neuroblastomas, 1 astroblastoma, 1 neuroepithelioma, and 14 gliomas of unspecified type.

‡The age of patients at the time of the interview was nearly identical to the age at the time of the diagnosis of the tumor (for patients with tumors) and the age at the time of hospital admission.

transportable cellular telephones did not (Fig. 1A). Use of hand-held cellular telephones was higher among men than among women, decreased with age for both sexes (but more so for women), and was positively associated with self-reported household income and educational level (Fig. 1B, 1C, and 1D). The lower prevalence of use among patients with circulatory disease reflects their older age (mean, 57 years, as compared with 47 years for other controls).

Risk According to Level of Use

Neither ever having used a hand-held cellular telephone nor regular use of one was significantly associated with the relative risk of glioma, meningioma, or acoustic neuroma (Table 2). Among regular users, relative risks were not higher among those who began using cellular telephones in earlier years, nor did the risk of any type of tumor increase significantly with increasing duration of use, frequency of use, or total cumulative use (Table 2).

Seventeen patients with tumors and 28 controls reported having used hand-held cellular telephones for an average of 15 or more minutes per day for at least three years. The distribution of these patients according to histologic type of tumor was as follows: four had anaplastic astrocytoma, three had glioblastoma, one

had astrocytoma, one had oligodendroglioma, one had ependymoma, two had an unspecified type of glioma, four had meningioma, and one had acoustic neuroma. The relative risk for glioma at this level of cellular-telephone use was 0.7 (95 percent confidence interval, 0.3 to 1.6).

Significantly elevated relative risks were not observed for any of the hospitals, for either sex, or for any age groups, and there was little heterogeneity in risk among subgroups of the controls (data not shown). For glioma, the relative risk associated with using a cellular telephone more than five times as compared with never using one was 1.2 when the control group used in the analysis was limited to persons admitted because of injuries; the relative risk was 1.0 when the subgroup was those admitted for circulatory diseases; 1.0 when the subgroup was those admitted for musculoskeletal diseases; and 0.9 when the subgroup was those admitted for other illnesses or conditions.

The relative risks were not significantly increased for subcategories of glioma defined according to histologic type, grade, laterality, or affected lobe of the brain (Table 3). Estimated relative risks were 1.1 for all astrocytic tumors combined and 0.9 for high-grade astrocytoma. Within the latter category, the relative risk was nonsignificantly greater than 1.0 for anaplastic astrocytoma and nonsignificantly less than 1.0 for glioblastoma. The relative risk of anaplastic astrocytoma was greater for persons who had used cellular telephones one to five times in their lives (relative risk, 2.6) than for persons who had used them more than five times (relative risk, 1.8).

Additional covariates (marital status, religion, type of health insurance, history of radiotherapy to the head or neck, and handedness) had little or no influence on the estimates of relative risk, nor did age when age categories smaller than 10 years were used. Patients with glioma were interviewed, on average, four months earlier than controls, but the analysis was adjusted for the date of the interview, so the trend over time in the use of cellular telephones was taken into account.

Laterality of Tumor and of Telephone Use

Among patients with tumors who reported having used hand-held cellular telephones regularly for at least six months before diagnosis, the laterality of the tumor was not significantly associated with the self-reported laterality of use of the cellular telephone (Table 4). Relative risks of gliomas involving the frontal, temporal, and parietal lobes were 1.0 (P=1.00), 0.9

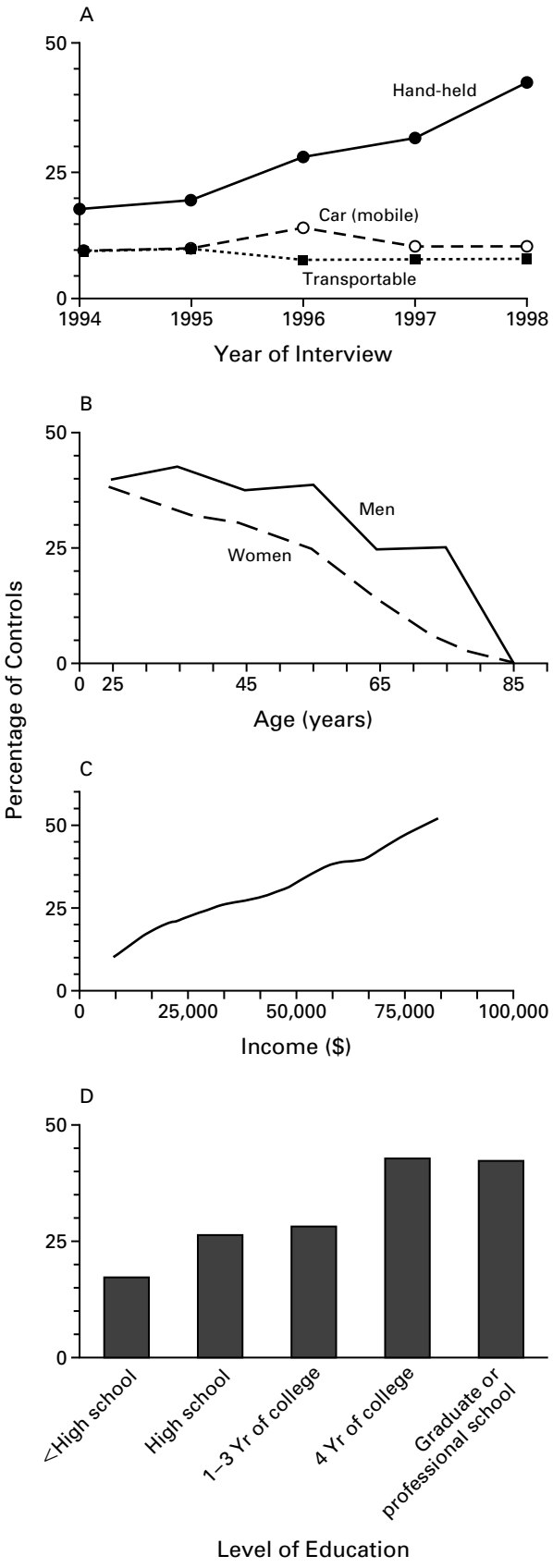

Figure 1. Percentage of Controls Who Had Used a Cellular Telephone More Than Five Times, According to the Year of the Interview and Type of Cellular Telephone (Panel A), Age at the Time of the Interview and Sex (Panel B), Self-Reported Annual Household Income (Panel C), and Level of Education (Panel D). Panels B, C, and D show the data for hand-held cellular telephones only.

TABLE 2. RELATIVE RISKS OF DIFFERENT TYPES OF INTRACRANIAL TUMOR OF THE NERVOUS SYSTEM, ACCORDING TO THE LEVEL OF USE OF HAND-HELD CELLULAR TELEPHONES.*

VARIABLE	CONTROLS	PATIENTS WITH GLIOMAS		PATIENTS WITH MENINGIOMAS		PATIENTS WITH ACOUSTIC NEUROMAS		ALL PATIENTS WITH BRAIN TUMORS	
	NO.	NO.	RELATIVE RISK (95% CI)	NO.	RELATIVE RISK (95% CI)	NO.	RELATIVE RISK (95% CI)	NO.	RELATIVE RISK (95% CI)
Use of hand-held cellular telephones									
No use†	440	285	1.0	130	1.0	56	1.0	471	1.0
Use	358	201	1.0 (0.7–1.4)	67	0.8 (0.5–1.2)	40	0.8 (0.5–1.4)	308	0.9 (0.7–1.1)
1 to 5 times in life	105	62	1.2 (0.8–1.8)	22	0.9 (0.5–1.7)	10	0.6 (0.2–1.3)	94	1.0 (0.7–1.4)
>5 times in life	232	121	0.9 (0.7–1.4)	43	0.7 (0.4–1.2)	30	1.0 (0.5–1.9)	194	0.9 (0.6–1.2)
Regular use	172	85	0.8 (0.6–1.2)	32	0.8 (0.4–1.3)	22	1.0 (0.5–1.9)	139	0.8 (0.6–1.1)
Average daily use‡									
Never or rarely used†	625	398	1.0	165	1.0	74	1.0	637	1.0
<3 min	53	27	0.9 (0.5–1.6)	9	0.7 (0.3–1.7)	7	1.0 (0.4–2.9)	43	0.8 (0.5–1.4)
3 to <15 min	64	37	1.0 (0.6–1.6)	13	1.2 (0.5–2.7)	10	1.4 (0.6–3.2)	60	1.1 (0.7–1.7)
≥15 min	51	20	0.5 (0.3–1.0)	10	0.7 (0.3–1.8)	5	0.9 (0.3–2.8)	35	0.6 (0.3–1.0)
≥60 min	24	12	0.7 (0.3–1.7)	5	0.5 (0.1–2.2)	1	0.3 (0.0–2.7)	18	0.6 (0.3–1.3)
Duration of regular use‡									
Never or rarely used†	625	398	1.0	165	1.0	74	1.0	637	1.0
<0.5 yr	56	24	0.6 (0.3–1.1)	6	0.5 (0.2–1.4)	4	0.3 (0.1–1.3)	34	0.6 (0.3–0.9)
0.5 to <3.0 yr	55	31	0.9 (0.5–1.6)	12	0.8 (0.4–1.9)	8	1.8 (0.7–4.5)	51	1.0 (0.6–1.6)
≥3.0 yr	60	30	0.9 (0.5–1.5)	14	1.1 (0.5–2.5)	10	1.4 (0.6–3.4)	54	1.0 (0.6–1.6)
≥5.0 yr	31	11	0.6 (0.3–1.4)	6	0.9 (0.3–2.7)	5	1.9 (0.6–5.9)	22	0.9 (0.5–1.6)
Cumulative use‡									
Never or rarely used†	625	398	1.0	165	1.0	74	1.0	637	1.0
<13 hr	55	26	0.8 (0.4–1.4)	8	0.7 (0.3–1.9)	5	0.7 (0.2–2.3)	39	0.7 (0.4–1.2)
13 to 100 hr	58	26	0.7 (0.4–1.3)	13	1.1 (0.5–2.4)	8	1.2 (0.5–3.1)	47	0.9 (0.6–1.4)
>100 hr	54	32	0.9 (0.5–1.6)	11	0.7 (0.3–1.7)	9	1.4 (0.6–3.5)	52	1.0 (0.6–1.5)
>500 hr	27	11	0.5 (0.2–1.3)	6	0.7 (0.2–2.4)	1	0.4 (0.0–3.3)	18	0.7 (0.2–1.1)
Year use began‡									
Never or rarely used†	625	398	1.0	165	1.0	74	1.0	637	1.0
1995 through 1998	61	24	0.8 (0.4–1.5)	14	1.1 (0.5–2.4)	7	0.7 (0.3–2.0)	45	0.9 (0.5–1.4)
1993 or 1994	60	38	1.0 (0.6–1.6)	8	0.5 (0.2–1.5)	9	1.5 (0.6–3.6)	55	0.9 (0.6–1.4)
≤1992	50	23	0.6 (0.3–1.1)	9	0.8 (0.3–2.0)	6	1.2 (0.4–3.4)	38	0.7 (0.4–1.2)
<1990	23	8	0.3 (0.1–1.0)	3	0.3 (0.1–1.6)	2	1.3 (0.2–6.6)	13	0.4 (0.2–0.9)

*All relative risks were adjusted for the matching variables (age, sex, race or ethnic group, hospital, and distance from the patient's residence to the hospital), education, self-reported annual household income, date of interview, and interview respondent. For acoustic neuroma, the relative risk was also adjusted for the median household income in the census tract where the patient lived. It was unknown whether one control and three patients with gliomas had ever used a hand-held cellular telephone. In addition, the number of times a cellular telephone was used was unknown for 21 controls, 18 patients with gliomas, and 2 patients with meningiomas, all of whom were known users. "Regular" use was defined as two or more calls per week. The "never or rarely used" category includes persons who used a cellular telephone fewer than five times in their lives and those who never used one on a regular basis. The cumulative use was calculated as the product of the duration of the period of regular use (in weeks) and the average hours per week of use during that time. CI denotes confidence interval.

†This group served as the reference group.

‡The categories were based on the distributions among controls. The difference between the total number in the three categories of regular use and the total number of regular users is due to some persons' reporting regular use but not specifying an amount of time of use.

(P=0.66), and 0.8 (P=0.55), respectively, and the relative risk of anaplastic astrocytoma was 1.2 (P=1.00).

DISCUSSION

Our results do not substantiate the concern that some brain tumors diagnosed in the United States during the mid-1990s were caused by the use of hand-held cellular telephones. There was little or no indication of an increased risk of glioma, meningioma, or acoustic neuroma associated with any use, cumulative use, or the laterality of use of these telephones. There was no significantly increased risk associated with the use of cellular telephones at any of the three centers, and estimates of the relative risk associated with the use of cellular telephones were insensitive to the inclusion or exclusion of any of the four principal subgroups of controls.

Some degree of misclassification of patients' relative levels of exposure was inevitable, because of inherent limitations in the ability of the interview to capture historical changes in a patient's pattern of cellular telephone use, inaccuracies in patients' recall, and variations in the levels of exposure to microwave radiation with different types of hand-held cellular telephones and under different circumstances of use. In a previous study,[29] a good correlation (Spearman's r=0.79) was reported between the self-reported use of cellular telephones and billing records from cellular-telephone companies. Patients with gliomas sometimes have impairments of memory or cognition that might com-

TABLE 3. RELATIVE RISKS OF GLIOMA AND NEUROEPITHELIOMATOUS TUMORS ASSOCIATED WITH THE USE OF HAND-HELD CELLULAR TELEPHONES MORE THAN FIVE TIMES, AS COMPARED WITH NO USE.*

VARIABLE	TOTAL	USE MORE THAN 5 TIMES	RELATIVE RISK (95% CI)
		no.	
All cases of glioma	489	121	0.9 (0.7–1.4)
High grade†	354	70	0.9 (0.6–1.4)
Low grade	135	51	1.0 (0.5–1.7)
Histologic type of tumor			
Astrocytoma (all grades)	345	69	1.1 (0.6–1.4)
Glioblastoma and gliosarcoma	241	33	0.8 (0.4–1.4)
Anaplastic astrocytoma	70	25	1.8 (0.7–5.1)
Other types	34	11	1.3 (0.4–4.1)
Oligodendroglioma and mixed glioma	85	31	0.7 (0.4–1.5)
Other and unspecified types of glioma	34	13	1.2 (0.3–4.6)
Neuroepitheliomatous tumors	25	8	0.5 (0.1–2.0)
Laterality of tumor‡			
Left	220	52	0.9 (0.6–1.5)
Right	223	53	0.8 (0.5–1.3)
Affected lobe§			
Frontal	220	60	0.9 (0.5–1.4)
Temporal	175	41	0.8 (0.5–1.4)
Parietal	135	30	1.1 (0.6–2.1)
Occipital	34	6	0.7 (0.2–2.5)

*All 799 controls (232 of whom used a hand-held cellular telephone more than five times) were used as the reference group for each subgroup of patients with tumors. The relative risks have been adjusted for the same covariates as in Table 2. CI denotes confidence interval.

†High-grade gliomas include glioblastomas, gliosarcomas, anaplastic astrocytomas, other anaplastic gliomas (grade III or IV on a four-point scale), astroblastomas, and embryonal tumors (medulloblastomas, primitive neuroectodermal tumors, and neuroblastomas).

‡Forty-six tumors were either centrally located or involved both sides of the brain and are therefore excluded.

§Tumors involving more than one lobe are included for each affected lobe. Tumors not involving the cerebral cortex are excluded.

TABLE 4. LATERALITY OF TUMOR WITH RESPECT TO LATERALITY OF TELEPHONE USE AMONG PATIENTS WITH BRAIN TUMORS WITH REGULAR USE OF A HAND-HELD CELLULAR TELEPHONE FOR AT LEAST SIX MONTHS BEFORE DIAGNOSIS.*

TYPE AND LATERALITY OF TUMOR	LATERALITY OF TELEPHONE USE			RELATIVE RISK†	P VALUE‡
	LEFT	RIGHT	TOTAL		
All types				0.9	0.51
Left	14	28	42		
Right	19	27	46		
Total	33	55	88		
Any glioma				0.9	0.77
Left	8	18	26		
Right	10	17	27		
Total	18	35	53		
Astrocytic glioma				0.9	1.00
Left	5	10	15		
Right	7	11	18		
Total	12	21	33		
Meningioma				0.9	1.00
Left	4	6	10		
Right	5	6	11		
Total	9	12	21		
Acoustic neuroma				0.9	0.63
Left	2	4	6		
Right	4	4	8		
Total	6	8	14		

*"Regular" use was defined as two or more calls per week. Patients with tumors whose tumor or telephone use was not exclusively attributed to one side or the other were excluded from the analysis.

†The relative risk of a brain tumor associated with cellular-telephone use was estimated as $[(\sqrt{OR}+1)\div 2]$, where OR denotes the odds ratio.

‡P values were based on Fisher's exact test.

promise their ability to report past events and habits as accurately as healthy persons. Such impairment is considerably less common among young and middle-aged patients with gliomas than among elderly patients and is uncommon among patients with meningiomas or acoustic neuromas.[26] Cellular-telephone use was much more common among persons less than 70 years old than among those 70 years old or older (Fig. 1B). If cellular telephones cause brain tumors, and the induction period is not long, one would expect the effect to be evident among case patients younger than the ages at which aphasia is a common symptom. It was not.

In addition to the frequency and duration of telephone use, factors that can affect the level of exposure to microwave radiation include the distance from the base station, the local topography and vegetation, whether the phone is used indoors or outdoors, the design of the particular model of telephone, and the position of the antenna and the telephone in relation to the head.[8,20,30,31] Failure to account for these variables could result in the misclassification of the level of exposure, but these factors are unlikely to vary systematically with the frequency or duration of use. The misclassification of the level of use is more likely than the misclassification of use itself, and the low overall risk among regular users suggests that if the study failed to detect a substantially elevated risk, it was confined to a small subgroup.

Microwave radiation is attenuated rapidly with passage though tissue, so that the absorption of energy by tissue 5 cm below the surface of the skin is less than 10 percent of that at the surface, and absorption is an order of magnitude less on the side of the head opposite that on which the telephone is used than it is on the side of use.[1,4,20,31-34] However, we found no positive associations between the laterality of the tumor and the side of cellular-telephone use for any of the principal categories of tumors. It is difficult to assess correlations between the location of the tumor and the deposition of microwave energy at a finer gradation than laterality, insofar as the pattern of energy absorption is sensitive even to small changes in the position and design of the telephone[32,35] and the pre-

cise origin of the tumor is unknown. Parts of the temporal, parietal, and occipital lobes have been described as regions of relatively high exposure, whereas the frontal lobe is generally considered to be much less exposed.[1,4,6,34] We found no evidence that cellular-telephone use was more strongly associated with gliomas in the temporal or parietal lobe than it was with gliomas in the frontal lobe.

The most important limitation of our study is its limited precision for assessing the risks after a potential induction period of more than several years or among people with very high levels of daily or cumulative use. For example, we cannot rule out a 60 percent increase in the risk of glioma associated with cumulative use of 100 hours or more. If an effect of cellular telephones was limited to a relatively uncommon type of tumor, or to a very small volume of highly exposed tissue immediately adjacent to the handset, a much larger sample would be required to detect it. The study was designed to have adequate power to assess the relative risk of all gliomas combined, but not for subtypes of glioma.

There have been substantial changes in wireless communication technology since this study began in 1993. The current trend is toward greater use of digital technology and higher frequencies of transmission.[8,20,36-38] Because of the timing of this study, we presume that our results pertain primarily to analogue telephones with frequencies of 800 to 900 MHz. Digital telephones operate at a lower average power than analogue telephones,[4,8] and we would not expect them to carry a higher risk, unless there is an important aspect of exposure other than the rate of energy deposition. No increase in the risk of brain tumors associated with the use of analogue or digital cellular telephones was found in a small, case–control study conducted in Sweden.[6] Multicenter, international studies that are just getting under way[39,40] will have greater statistical power to assess the risks of cancer associated with long induction periods and will provide information about the risks associated with the use of digital telephones.

Our results do not support the view that exposure to low-power microwave radiation from hand-held, analogue cellular telephones causes malignant or benign tumors of the brain or nervous system. However, given the fact that widespread use of cellular telephones is a recent development, the dramatic increases that have occurred in the frequency of use, and the changes in cellular technology over time, the findings should be seen as an estimate of the risk at an early stage of the use of this technology.

We are indebted to our external advisory panel for their thoughtful comments and advice concerning the manuscript; to Emily Khoury, Brian Paul, Patsy Thompson, Donna Houpt, Kelli Williamson, Sandra McGuire, Renee Karlsen, Patricia Yost, Janice Whelan, Douglas Watson, Diane Fuchs, Bob Saal, Christel McCarty, George Geise, and Rebecca Albert for their valuable and dedicated assistance during the conduct of the study; and to the University of North Carolina Hospitals for providing the opportunity to pretest study instruments and procedures on a sample of neurosurgical patients.

APPENDIX

Statistical Issues Related to Laterality of Tumor and Side of Cellular-Telephone Use

In the following analysis, B denotes brain tumor, P cellular-telephone use, R right side, L left side, and Pr probability. The usual estimate of the odds ratio from a two-by-two table for laterality like those in Table 4 is an estimate of the quantity

$$[\Pr(B^R|P^R)\Pr(B^L|P^L)]\div[\Pr(B^L|P^R)\Pr(B^R|P^L)],$$

where, for example, $\Pr(B^R|P^R)$ is the probability of the development of a brain tumor on the right side of the brain when the cellular telephone was used on the right side. If cellular-telephone use is independent of the risk of brain tumors, then

$$\Pr(B^R|P^R)=\Pr(B^R|P^L)=\Pr(B^R) \text{ and } \Pr(B^L|P^L)=\Pr(B^L|P^R)=\Pr(B^L),$$

so that the odds ratio is always 1.0, even though there may be a higher probability that a tumor will develop on one side of the brain than the other.

Suppose that cellular-telephone use is associated with brain tumors and that the relative risk that a tumor will develop on the side of cellular-telephone use is the same for tumors on the left side and on the right side. That is, assume that

$$\Pr(B^L|P^L)=\Theta\ \Pr(B^L|P^R) \text{ and } \Pr(B^R|P^R)=\Theta\ \Pr(B^R|P^L).$$

It follows that the usual odds ratio estimated from a two-by-two table for laterality is an estimate of Θ^2, and thus that the square root of the odds ratio is an estimate of Θ. If cellular-telephone use does not expose the side of the brain opposite the side of use to any radiation, then the laterality risk ratio, Θ, quantifies the risk of brain tumors due to cellular-telephone use.

The relative risk for the general population is defined as

$$RR=P(B|P)\div P(B|\text{no P}),$$

where brain tumors and cellular-telephone exposure can occur on either side of the brain. Assume that brain tumors are equally likely on the left and the right side in the absence of cellular-telephone exposure. Then it follows that

$$\begin{aligned}\Pr(B|\text{no P})&=\Pr(B^R|\text{no P})+\Pr(B^L|\text{no P})=2\Pr(B^R|\text{no P})\\&=2\ \Pr(B^R|P^L)=2\ \Pr(B^L|P^R).\end{aligned}$$

Assuming, without loss of generality, that cellular-telephone use is on the left side, it follows that

$$\Pr(B|P)=\Pr(B|P^L)=\Pr(B^L|P^L)+\Pr(B^R|P^L),$$

and thus that $RR=(\Theta+1)\div 2$.

REFERENCES

1. Balzano Q, Garay O, Manning TJ Jr. Electromagnetic energy exposure of simulated users of portable cellular telephones. IEEE Trans Veh Technol 1995;44:390-403.

2. How many people use wireless phones? Washington, D.C.: Cellular Telecommunication Industry Association, 2000. (See http://www.wow-com.com/consumer/faqs/faq_general.cfm#one.) (See NAPS document no. 05580 for 3 pages, c/o Microfiche Publications, 248 Hempstead Tpke., West Hempstead, NY 11552.)

3. Maier M, Blakemore C, Koivisto M. The health hazards of mobile phones. BMJ 2000;320:1288-9.

4. Rothman KJ, Chou CK, Morgan R, et al. Assessment of cellular telephone and other radio frequency exposure for epidemiologic research. Epidemiology 1996;7:291-8.

5. McKinlay A. Possible health effects related to the use of radiotelephones: recommendations of a European Commission Expert Group. Radiol Prot Bull 1997;187:9-16.

6. Hardell L, Näsman Å, Påhlson A, Hallquist A, Hansson Mild K. Use of cellular telephones and the risk for brain tumours: a case-control study. Int J Oncol 1999;15:113-6.

7. Moulder JE, Erdreich LS, Malyapa RS, Merritt J, Pickard WF, Vijayalaxmi. Cell phones and cancer: what is the evidence for a connection? Radiat Res 1999;151:513-31.

8. Independent Expert Group on Mobile Phones. Mobile phones and health. Chilton, England: National Radiological Protection Board, 2000.

9. Hermann DM, Hossmann K-A. Neurological effects of microwave exposure related to mobile communication. J Neurol Sci 1997;152:1-14.
10. Anderson V, Joyner KH. Specific absorption rate levels measured in a phantom head exposed to radio frequency transmissions from analog hand-held mobile phones. Bioelectromagnetics 1995;16:60-9.
11. Valberg PA. Radio frequency radiation (RFR): the nature of exposure and carcinogenic potential. Cancer Causes Control 1997;8:323-32.
12. Van Leeuwen GMJ, Lagendijk JJW, Van Leersum BJAM, Zwamborn APM, Hornsleth SN, Kotte ANTJ. Calculation of change in brain temperatures due to exposure to a mobile phone. Phys Med Biol 1999;44:2367-79.
13. Adey WR. Bioeffects of mobile communications fields: possible mechanisms for cumulative dose. In: Kuster N, Balzano Q, Lin JC, eds. Mobile communications safety. New York: Chapman & Hall, 1997:95-131.
14. Meltz ML, Walker KA, Erwin DN. Radiofrequency (microwave) radiation exposure of mammalian cells during UV-induced DNA repair synthesis. Radiat Res 1987;110:255-66.
15. Brusick D, Albertini R, McRee D, et al. Genotoxicity of radiofrequency radiation. Environ Mol Mutagen 1998;32:1-16.
16. Malyapa RS, Ahern EW, Straube WL, Moros EG, Pickard WF, Roti Roti JL. Measurement of DNA damage after exposure to electromagnetic radiation in the cellular phone communication frequency band (835.62 and 847.74 MHz). Radiat Res 1997;148:618-27.
17. Dreyer NA, Loughlin JE, Rothman KJ. Cause-specific mortality in cellular telephone users. JAMA 1999;282:1814-6.
18. Elwood J. A critical review of epidemiologic studies of radiofrequency exposure and human cancers. Environ Health Perspect 1999;107:Suppl 1: 155-68.
19. Morgan RW, Kelsh MA, Zhao K, Exuzides KA, Heringer S, Negrete W. Radiofrequency exposure and mortality from cancer of the brain and lymphatic/hematopoietic systems. Epidemiology 2000;11:118-27.
20. International Commission on Non-Ionizing Radiation Protection. Health issues related to the use of hand-held radiotelephones and base transmitters. Health Phys 1996;70:587-93.
21. Repacholi MH. Low-level exposure to radiofrequency electromagnetic fields: health effects and research needs. Bioelectromagnetics 1998;19: 1-19.
22. Electromagnetic fields (300 Hz to 300 GHz). Geneva: World Health Organization, 1993.
23. Inskip PD, Hatch EE, Stewart PA, et al. Study design for a case-control investigation of cellular telephones and other risk factors for brain tumors in adults. Radiat Prot Dosim 1999;86:45-52.
24. Percy C, Van Holten V, Muir C, eds. International classification of diseases for oncology, 2nd ed.: ICD-O. Geneva: World Health Organization, 1990.
25. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. Brain Pathol 1993;3:255-68.
26. Kleihues P, Cavenee WK. Pathology and genetics of tumours of the nervous system. Lyon, France: International Agency for Research on Cancer, 1997.
27. Lubin JH. A computer program for the analysis of matched case-control studies. Comput Biomed Res 1981;14:138-43.
28. Preston DL, Lubin JH, Pierce DA, McConney ME. Epicure users guide. Seattle: Hirosoft International, 1993.
29. Funch DP, Rothman KJ, Loughlin JE, Dreyer NA. Utility of telephone company records for epidemiologic studies of cellular telephones. Epidemiology 1996;7:299-302.
30. Cleveland RF Jr, Athey TW. Specific absorption rate (SAR) in models of the human head exposed to hand-held UHF portable radios. Bioelectromagnetics 1989;10:173-86.
31. Balzano Q. Exposure metrics for RF epidemiology: cellular phone handsets. Radiat Prot Dosim 1999;83:165-9.
32. Gandhi O. Some numerical methods for dosimetry: extremely low frequencies to microwave frequencies. Radio Sci 1995;30:161-77.
33. Dimbylow PJ, Mann SM. SAR calculations in an anatomically realistic model of the head for mobile communication transceivers at 900 MHz and 1.8 GHz. Phys Med Biol 1994;39:1537-53.
34. Dimbylow P, Mann SM. Characterization of energy deposition in the head from cellular phones. Radiat Prot Dosim 1999;83:139-41.
35. Kuster N, Balzano Q. Experimental and numerical dosimetry. In: Kuster N, Balzano Q, Lin JC, eds. Mobile communications safety. New York: Chapman & Hall, 1997:13-64.
36. Dreyer NA, Loughlin JE, Rothman KJ. Epidemiological safety surveillance of cellular telephones in the US. Radiat Prot Dosim 1999;83:159-63.
37. Ramsdale PA, Wiener A. Cellular phone base stations: technology and exposures. Radiat Prot Dosim 1999;83:125-30.
38. Millington RJ. Mobile and personal communications in the 90s. In: Kuster N, Balzano Q, Lin JC, eds. Mobile communications safety. New York: Chapman & Hall, 1997:3-9.
39. Of mobile phones and morbidity. Environ Health Perspect 1998;106: A474-A475.
40. Cardis E, Kilkenny M. International case-control study of adult brain, head and neck tumours: results of the feasibility study. Radiat Prot Dosim 1999;83:179-83.