THE YALE JOURNAL OF BIOLOGY AND MEDICINE 59 (1986), 517-531

Multiple Primary Malignant Neoplasms in England and Wales, 1971-1981

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Received December 9, 1985

In the period 1971-81, more than 1.9 million persons were registered with a malignant neoplasm among the 49.2 million population of England and Wales. For 63,536 people, two or more tumor registrations (multiple tumor records) have arisen in that period. Because of the structure of the National Cancer Registration scheme, some errors in registration are inevitable, particularly duplicate registration of a single tumor by adjacent regional cancer registries. A pilot study showed that 61 percent of multiple records would represent true multiple primary malignancy, and that these records could be readily separated from registration errors.

After abstraction of identifying codes from each tumor, 129,047 tumors involved in 63,536 multiple records were matched to the national cancer file, and the full data set extracted for successfully matched tumors. Person-years data were extracted for the 1.8 million tumors not involved in a multiple record. Eleven percent of multiple records were not completely matched, and a further 16 percent were excluded on SEER criteria, or as probable registration errors, leaving 46,155 multiple primary tumors for further analysis. Over 3 million person-years at risk of a second tumor were accrued. The overall risk of a second tumor at any site before age 85 was 0.77 for males and 0.80 for females, after exclusion of second tumors observed within 12 months of the first. The risk of a new primary apparently decreased with increasing duration of survival, a trend which may be due in part to under-registration of second tumors in the early 1970s and an improvement in linkage since 1971.

INTRODUCTION

The study of multiple primary malignant neoplasms may provide information relevant both to the etiology and to the management of cancer [1]. In discussing the incidence of bilateral breast tumors, Prior and Waterhouse [2] comment that "knowledge of absolute and differential rates of second primary tumours is not only of great clinical importance for the future management of the breast cancer patient, but might give some clues to the aetiology of the disease itself"; their remark has a wider relevance for second malignancies in general.

Two malignant tumors arising in one individual may share a common genetic predisposition, as with retinoblastoma, or a common environmental etiology, as with bladder and respiratory tract tumors associated with the use of tobacco. Studying the association of two or more tumors in multiple primary neoplasia may therefore offer new clues to the etiology of cancer. The management of patients with one tumor may also be improved if those at highest risk of a second tumor can be identified from such studies, leading to appropriate surveillance and earlier, more effective treatment for the second tumor. The therapy for a first tumor has itself been recognized as an

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important cause of second primary neoplasms [3,4]: study of multiple primary tumors may be expected both to improve the choice of therapy for a first tumor and to identify the most probable site or type of a second primary for the purposes of surveillance.

The occurrence of two or more primary neoplasms in one individual may also be the result of chance. Study of this condition therefore requires access to a large body of data, because only a small proportion (perhaps 1 in 20) of patients with one malignancy will be expected to develop a second. In attempting to derive unbiased estimates of the incidence of second tumors, the individuals studied should be an unbiased sample—preferably a complete (100 percent) sample—of the population with a first tumor. A series of patients treated at a large hospital specializing in cancer therapy is unlikely to be representative of cancer patients as a whole, whether for site or stage of disease, or for other prognostic factors, unless the hospital treats *all* cancer patients in its territory.

Population-based data on the incidence of second malignancies remain scanty. Schoenberg [5] has provided evidence from the Connecticut Tumor Registry that patients with one cancer have 1.29 times the risk of developing a new primary cancer compared with individuals who never had cancer, studying over 5,000 second tumors registered in 30 years (1935–64) among 121,000 cancer patients. The risk was 1.37 for females and 1.20 for males. A study of 5,300 second cancers observed among 180,000 women treated for cervix cancer and registered at one of 15 population-based regional or national registries has been reported [6]. Recently Teppo et al. [7] reported 5,000 second cancers among nearly 280,000 cancer patients registered in the Finnish Cancer Registry from 1953–79. They noted an inverse relation between second tumor risk and age at first cancer, and the risk in females (1.09) was higher than for males (0.89), but their overall risk (0.99) did not confirm the overall result from the Connecticut Registry.

In England and Wales, fourteen[1] population-based regional cancer registries have covered the entire population since 1962 (Fig. 1). The Office of Population Censuses and Surveys (OPCS) collates registration data from all these registries to produce national incidence figures: about 200,000 tumors are registered annually. Each registry aims to record all new primary malignancies arising in residents of its territory and can usually link the records of two or more cancers in the same individual. Until recently, population-based studies of multiple primary malignancy in England and Wales would have been feasible only within regional registries; Prior and Waterhouse have published several such studies from the West Midlands registry [2,8–10]. But the population available to any one regional registry is relatively small; not all registries have computerized records or separate files for multiple cancer; record linkage efficiency varies among registries; and people who migrate across registry boundaries in the interval between their first and second cancer would not be detected as having multiple cancer.

From 1971, however, the National Cancer Registration scheme was modified, in order to obtain automatic survival data, by linking all new cancer registrations and death certifications on a single alphabetic index, the National Health Service Central Register (NHSCR) at Southport. There was an unexpected by-product of the new scheme. If, instead of death, the next vital event in a cancer patient was another cancer registration, the system now produced a multiple tumor record, evidence of multiple

[1]The three Thames registries amalgamated on 1 January 1985; there are now only 12 registries.

FIG. 1. Cancer registries in England and Wales; the three Thames registries amalgamated in 1985.

cancer (Fig. 2). Multiple records were returned to OPCS and stored. This change accidentally removed most of the problems of studying multiple cancer in regional registries. Linkage efficiency was high and largely independent of the cancer registry concerned; multiple cancer in migrants would be detected; and, above all, the entire national population was covered. But the scheme was not designed to detect multiple cancer, and errors of registration, particularly duplicate registration of a single tumor, either within one registry or between two registries, also gave rise to multiple tumor records. This report describes an attempt to exploit the National Cancer Registration scheme of England and Wales to study multiple primary cancer.

POPULATION AND METHODS

Regional cancer registries receive tumor notifications from hospitals and general practitioners, and copies of death certificates mentioning cancer for residents of their territory. Each registry maintains an alphabetic index, which serves both to avoid duplicate registration of a single tumor and to link two tumors in one person. However, a patient treated in two centers either side of a registry boundary will occasionally be registered in both registries.

The 1981 census population of England and Wales was 49.244 million. In the 11 years 1971–81, more than 1.9 million tumors among this population were flagged[2] at The National Health Service Central Register (NHSCR), excluding those registered at death or in non-residents. During this period, 63,536 multiple tumor records have

[2]Flagging an individual at NHSCR ensures automatic notification of death (1939–) and of any cancer registration (1971–).

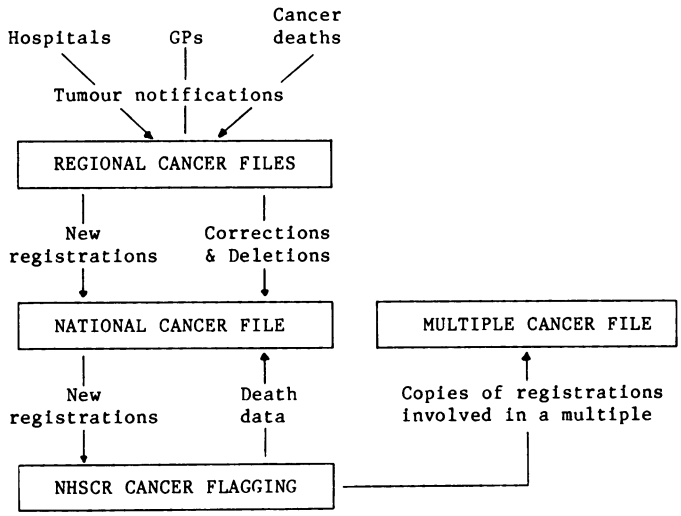

FIG. 2. Scheme of cancer registration in England and Wales.

arisen (by October 1984 the figure exceeded 100,000). A multiple tumor record is defined in this context as two or more tumor registrations linked at NHSCR to the same individual, each registered between 1 January 1971 and 31 December 1981.

A random 1 percent sample of multiple records for the decade 1971–80 was examined in detail, with the registry or registries involved. This pilot study showed that 86 percent of multiple records involving a single registry represented multiple primary malignant neoplasms, while the corresponding figure for those involving two or more registries was only 8 percent (Table 1). Duplicate registrations of a single tumor accounted for most of the remainder, but a third of the duplicates involving only a single registry had been detected and cancelled by the registry concerned. Faulty registration of metastases from a previously registered tumor accounted for 2 percent of the multiple records. No instance was found of linkage error, i.e., two tumors in different persons wrongly linked to one person's record.

TABLE 1
Results of 1 Percent Sample Study: Multiple Record Category by Registry Involvement

	All Records	One Registry	Two Registries
Number of records	398[a]	283	115
Percentage classified as:			
Multiple primary	64	86	8
Duplicate	34	11	89
Metastases	2	2	3
Linkage error	0	0	0
Other	1	1	1

[a]Excludes 50 records; 32 from N-E Thames registry, which suspended operation during the pilot study, and 18 for which all but one tumor registration had already been detected as an error and cancelled by the registry concerned. At the time of survey, only the estimated number (44,800) of multiple records for 1971–80 was available, hence sample size of 448.

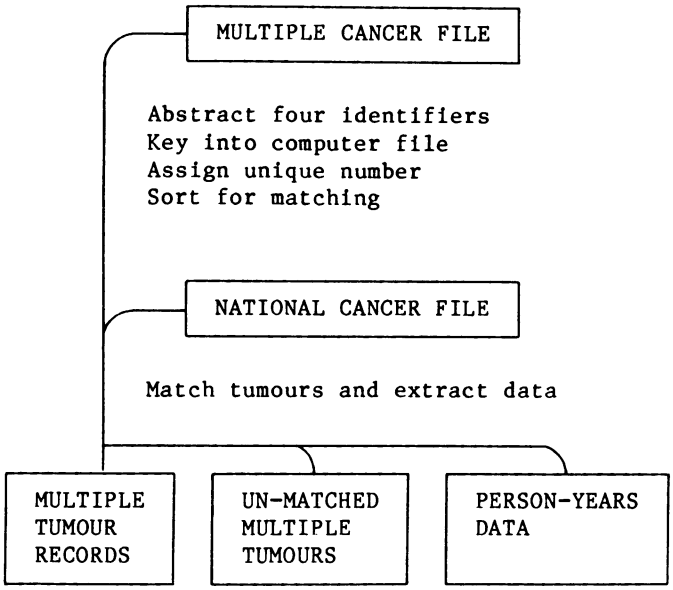

FIG. 3. Scheme for extraction of multiple tumor data.

This pilot survey showed that at least 64 percent of all the multiple records could be expected to be multiple primary neoplasms, and that most registration errors could be removed using criteria applicable within a computer program.

Four key identifiers (year of registration, code identifying the registry, tumor serial number within that registry, and anniversary date of the tumor) were abstracted from each tumor registration in each multiple record and entered into a computer file. A new multiple tumor number was automatically assigned to each tumor, consisting of a serial number from 1 to N, with a terminal digit representing the ordinal rank (1st, 2nd, 3rd, and so on) of each tumor within each multiple record. The resulting file, containing 63,536 multiple tumor records involving 129,047 registrations, was then sorted into the same sequence as the national cancer file and matched against it (Fig. 3). Three files resulted. Where all four identifiers on a tumor from a multiple record matched perfectly with a tumor on the national file, all the data on that tumor were extracted. Tumors from the multiple file for which a perfect match could not be found were stored separately. For tumors on the national file not involved in a multiple record, sufficient data were extracted to derive the person-years[3] at risk of a second tumor. Individuals were censored on reaching their hundredth birthday, if this preceded death, emigration, or the end of the study period on 31 December 1981.

Multiple records for which all component tumor registrations were successfully matched to an extant registration on the national cancer file were submitted to two further sets of checks. First, they were searched for probable errors of registration or linkage, using criteria derived from the pilot study. For example, multiple records involving two regional registries were excluded (unless they had previously been edited at OPCS to remove duplicates) because the pilot study had shown that only 8 percent

[3]Person-years: the sum of the (variable) number of years for which each person was followed up, i.e., observed whilst at risk of a second tumor. More appropriate than just the number of persons for use as the denominator of (second cancer) incidence rates, since some are observed only briefly, others for many years.

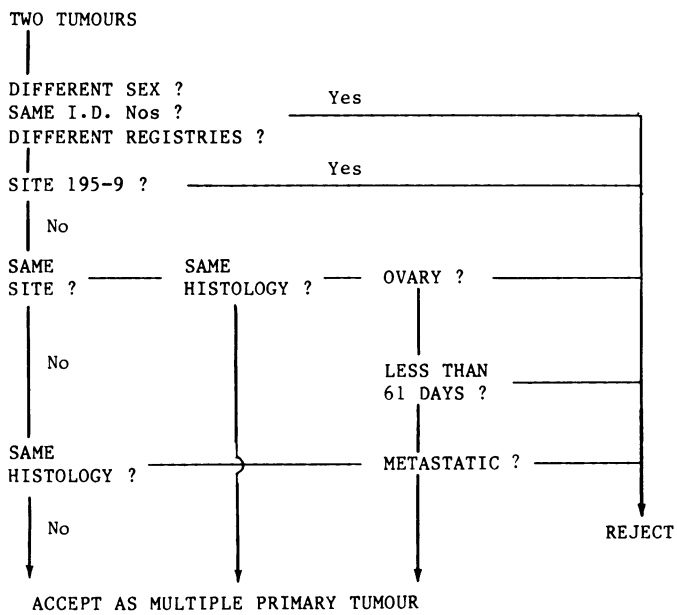

FIG. 4. Multiple primary tumor algorithm, designed to remove administrative registration errors and to apply SEER criteria for multiple primary tumors. Horizontal paths for "Yes"; vertical paths for "No."

were likely to represent multiple primary malignancy. Next, the records were checked with an algorithm designed to apply the Surveillance, Epidemiology and End Results program (SEER) criteria for multiple primary malignancy [11]. For this purpose, site was defined at the three-digit level of the eighth revision of the International Classification of Diseases (ICD) [12], after conversion [13] of ninth revision codes [14] for 1979–81. Records in which one or both of the tumors had been assigned a non-specific site-code (195-9) were excluded. For colon, rectum, bone, connective tissue and skin, site was defined at the four-digit level. Histology was defined at the three-digit level. A simplified schema of the algorithm used to apply these checks and exclusions is given in Fig. 4.

Expected numbers of second tumors were calculated by multiplying the age, sex, and calendar year-specific incidence rate for the second cancer site of interest by the person-years accrued by individuals with the first cancer within the same categories of age, sex, and time, then summing across all age groups and calendar years. Expected numbers are then compared with the observed number of second tumors. The result is a set of relative risks (observed/expected) for a particular second tumor among those with a given first tumor, for each sex and for each combination of two tumor sites, adjusted for age, calendar time, and survival from the first tumor. Such results can be examined separately for various time periods since each subject's first tumor (the interval at risk of a second tumor) to see if second cancer risk changes as survival increases.

The assumption underlying such calculations is that the risk of a tumor does not change appreciably within the age strata used; five-year age intervals are sufficiently small for this purpose for most tumors, but infants under one year of age are considered separately. Under the null hypothesis that the two tumors are rare independent events, the number of observed tumors can be treated as a random variable drawn from a Poisson distribution with mean equal to the expected number. The significance of any excess of observed tumors is assessed accordingly.

TABLE 2
Editing of Multiple Tumor Records

Original data		63,536
Not matched	1,092	
Partially matched	5,766	
Acceptable sequences		56,678
Sex error	207	
Two registries	5,291	
Ill-defined site	1,983	
Duplicates	2,988	
Metastases	54	
Multiple primary tumors		46,155

RESULTS

For 1,092 of the 63,536 original multiple records, neither of the tumors in the pair could be matched (Table 2), either because the tumor registration(s) had been previously cancelled or because of keying errors in preparation of the multiple file. These records will be reviewed in due course but are not considered further here. For a further 5,766 multiple records, one or more tumor registrations was successfully matched and extracted, but at least one was not. These records contain defective sequences of tumors (1–3; 2–3, and so on) and are also excluded from further consideration here.

A total of 56,678 multiple tumor records were fully matched to extant registrations on the national cancer file. These were further edited using the algorithm (Fig. 4). Different sex codes were found within 207 multiple records: these were excluded as possible linkage errors (Table 2). Records involving two or more registries were also excluded (see Methods). About 400 (8 percent) true multiple primaries may have been rejected among the 5,291 records in this category: they will be retrieved for analysis after further checks have been carried out. Almost 2,000 records involving a first or second tumor site-coded to 195-9 (ill-defined or secondary neoplasms) were excluded. Nearly 3,000 further records were rejected on the basis of SEER criteria involving site, histology, and time, and a further 54 because one of the first two tumors was coded as metastatic.

After removal of 10,523 records in this way, 46,155 multiple tumor records were considered acceptable for further analysis as multiple primary malignancies. These records contained two or more tumors satisfying the SEER definition of multiple primary malignancy, summarized in Table 3.

The distribution of first and second tumors by year of occurrence is shown in Table 4. The largest number of second tumors occurs in the same year as the first, with a gradual decline in successive years. More than a third of all second tumors arise in the same calendar year as the first, but this is largely a function of the relatively short follow-up (11 years at most), and the proportion falls to one-sixth where up to ten years of follow-up are available. This pattern appears more clearly in Table 5, where the number of second tumors arising with a given delay since the first tumor is seen to be fairly stable, regardless of the calendar year in which the first tumor was registered.

The distributions of first and second tumors in a multiple primary by broad site-group and by individual site are given in Tables 6 and 7, respectively. First tumors in a given site-group or site may be linked with second tumors at any site, and vice

TABLE 3
Criteria for Multiple Primary Malignancy

1. Neither tumor has non-specific site code (195-9).
2. Tumors are at different sites
   and either have different histology
   or same histology *and*
   neither is metastatic

OR

Tumors are at same site
   and either have different histology
   or same histology *and*
   neither is metastatic *and*
   they are more than 60 days apart.

versa: thus over 7,700 tumors of the digestive tract were observed as first tumors in a multiple primary followed by a second tumor at any site, while more than 11,000 tumors of the digestive tract occurred as second tumors, preceded by a first tumor at any site. These tables show that considerable numbers of multiple tumors are available for study at most sites: for example, more than 1,100 second leukemias.

Person-years at risk of a second tumor were accrued by almost 1.9 million individuals: their distribution by sex and by time since diagnosis of the first tumor is given in Table 8. Excluding the first twelve months since diagnosis, more than 2.75 million person-years were observed, almost three-quarters (73 percent) of these before the fifth anniversary of diagnosis of the first tumor. Only 16,000 person-years were accrued beyond the tenth anniversary: all these would be in subjects whose first tumor was diagnosed in 1971 and survived until some time in 1981 or beyond. At this stage, therefore, the available information on second cancer risk beyond ten years of follow-up will be scanty.

Results for second malignant tumors at any site (ICD-8 140-209) following a first malignant tumor at any site are presented in Table 9, for males and females up to the age of 84. Simultaneous tumors are excluded from this table (2,717 and 2,371 for males and females, respectively). A total of 11,159 second tumors were observed in males at least 12 months after the first tumor, against 14,424.5 expected, an overall risk of 0.77. Among females, there were 9,538 observed against 11,883.6 expected second tumors between one and 11 years after the first tumor, an overall risk of 0.80. For both sexes, the second tumor risk exceeded unity in the twelve months immediately after diagnosis of the first tumor and was less than unity thereafter. For each sex, there is a downward trend of second cancer risk with time. Each individual risk estimate is significantly different from unity ($p < 0.01$) and each time trend is also significant ($p < 0.001$).

DISCUSSION

Review of a 1 percent random sample of an estimated 44,800 multiple tumor records arising in England and Wales during the period 1971–1980 had shown that 64 percent could be expected to represent multiple primary malignancy; the proportion would be much higher (86 percent) among multiple records for which all the tumors originated from a single registry. The review also showed that more than 100,000 such records had arisen by the end of 1984, and that it would be feasible to separate registration errors from multiple primary cancers [15].

TABLE 4
First and Second Tumors by Year of Registration

Year of First Tumor	Year of Second Tumor											
	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	Total
1971	854	521	512	509	444	411	352	302	287	265	201	4,658
1972	—	904	669	630	497	467	414	357	325	316	250	4,829
1973	—	—	1,264	912	633	526	475	414	329	387	254	5,194
1974	—	—	—	1,884	970	660	594	469	423	394	295	5,689
1975	—	—	—	—	1,647	891	628	555	467	480	350	5,018
1976	—	—	—	—	—	2,101	932	687	508	551	421	5,200
1977	—	—	—	—	—	—	1,754	857	594	598	473	4,276
1978	—	—	—	—	—	—	—	1,639	852	712	516	3,719
1979	—	—	—	—	—	—	—	—	1,594	1,096	553	3,243
1980	—	—	—	—	—	—	—	—	—	2,068	899	2,967
1981	—	—	—	—	—	—	—	—	—	—	1,362	1,362
Total	854	1,425	2,445	3,935	4,191	5,056	5,149	5,280	5,379	6,867	5,574	46,155

TABLE 5
Multiple Tumors by Interval Between First and Second Tumor

Year of First Tumor	Years Between First and Second Tumor											Total
	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–	10–11	
1971	1,145	501	498	516	390	392	326	280	277	242	91	4,658
1972	1,273	625	588	447	434	403	337	327	276	119	—	4,829
1973	1,808	690	577	516	427	359	372	323	122	—	—	5,194
1974	2,476	702	638	562	416	421	342	132	—	—	—	5,689
1975	2,158	708	582	505	491	422	152	—	—	—	—	5,018
1976	2,665	747	584	508	478	218	—	—	—	—	—	5,200
1977	2,225	691	581	566	213	—	—	—	—	—	—	4,276
1978	2,145	726	604	244	—	—	—	—	—	—	—	3,719
1979	2,244	762	237	—	—	—	—	—	—	—	—	3,243
1980	2,614	353	—	—	—	—	—	—	—	—	—	2,967
1981	1,362	—	—	—	—	—	—	—	—	—	—	1,362
Total	22,115	6,505	4,889	3,864	2,849	2,215	1,529	1,062	675	361	91	46,155
Annual average	2,010	651	543	483	407	369	306	266	225	181	91	4,616

TABLE 6
Multiple Tumors by Site-Group

ICD-8	Site-Group	First Tumors	Second Tumors
150-8	Digestive	7,728	11,129
160-2	Respiratory	4,789	8,843
170-2	Bone, soft, skin	847	729
180-4	Female genital	3,424	3,256
200-2	Lymphomas	976	1,121
204-7	Leukemias	1,012	1,187
140-239	All sites	46,155	46,155

TABLE 7
Multiple Tumors by Site

ICD-8	Site	First Tumors	Second Tumors
140	Lip	285	124
141	Tongue	211	177
142	Salivary gland	173	136
143	Gum	83	60
144	Floor of mouth	110	92
145	Mouth, NOS	143	115
146	Oropharynx	141	123
147	Nasopharynx	47	54
148	Hypopharynx	113	125
149	Pharynx, NOS	50	53
150	Esophagus	468	963
151	Stomach	1,210	2,556
152	Small intestine	107	132
153	Colon	3,064	3,602
154	Rectum	2,206	2,219
155	Liver	124	217
156	Gall bladder	127	244
157	Pancreas	355	1,112
158	Peritoneum	67	84
159	Digestive, NOS	22	51
160	Nose, sinuses	149	121
161	Larynx	819	480
162	Trachea, bronchus	3,821	8,242
163	Respiratory, NOS	73	101
170	Bone	74	103
171	Connective, soft tissue	252	224
172	Melanoma	521	402
173	Other skin	10,843	5,659
174	Breast (M and F)	5,499	4,237
180	Cervix	952	685
181	Chorionepithelioma	4	10
182	Uterus, other	1,254	1,020
183	Ovary	939	1,223
184	Other female genital	275	318

TABLE 7—*continued*

ICD-8	Site	First Tumors	Second Tumors
185	Prostate	2,081	2,365
186	Testis	92	71
187	Other male genital	125	82
188	Bladder	3,157	2,588
189	Other urinary	760	939
190	Eye	118	83
191	Brain	205	336
192	Other CNS	77	63
193	Thyroid	168	171
194	Other endocrine	55	61
200	Lymphosarcoma	391	445
201	Hodgkin's disease	252	187
202	Other lymphoid	333	489
203	Myeloma	306	383
204	Lymphatic leukemia	699	585
205	Myeloid leukemia	215	440
206	Monocytic leukemia	18	41
207	Other leukemia	80	121
208	Polycythemia vera	187	61
209	Myelofibrosis	88	40
–	Benign, in situ, etc.	2,167	1,540
140-209	Total malignant	43,988	44,615
140-239	All registrations	46,155	46,155

Data were extracted from national cancer files for more than 56,000 complete sequences of tumors, of which 46,155 appear to be multiple primary malignancies. The distribution of these tumors by site and by time is consistent with what would be expected for multiple primary malignancies. To be included in the data, both the first and the second tumor had to be registered in the 11-year interval 1971–81. During that period there was a steady decline in the annual number of first tumors involved in a multiple primary by 1981 (Fig. 5). There was a parallel increase in the annual number of second tumors, as the total population at risk of a second tumor since 1971 gradually increased (Table 4).

The pattern of occurrence by year and by period at risk (Tables 4 and 5) suggests

TABLE 8
Person-Years at Risk (1971–81) by Sex and Time Since First Tumor

Category	Years Since Diagnosis of First Tumor				
	0–	1–4	5–9	10–11	Total[a]
Male	510,004.8	805,173.9	269,910.7	5,947.2	1,081,031.8
Female	617,638.5	1,212,625.9	449,995.1	10,090.8	1,672,711.8
Total	1,127,643.3	2,017,799.8	719,905.8	16,038.0	2,753,743.6

[a]Excluding first year of follow-up.

TABLE 9
Second Malignant Tumors (Any Site), Following a First Malignant Tumor (Any Site), England and Wales, 1971–81: Males and Females Aged 0–84

	Years Since Diagnosis of First Tumor				
	0–	1–4	5–9	10–11	Total[a]
		Males			
Person-years (thousands)	480.0	743.8	245.9	5.4	995.2
Observed	7,876	8,487	2,632	40	11,159
Expected	6,818.7	10,660.6	3,677.9	86.0	14,424.5
Relative risk	1.16	0.80	0.72	0.47	0.77
		Females			
Person-years (thousands)	555.9	1,063.0	380.0	8.3	1,451.2
Observed	6,217	7,176	2,327	35	9,538
Expected	4,420.0	8,575.2	3,235.8	72.6	11,883.6
Relative risk	1.41	0.84	0.72	0.48	0.80

[a]Excluding the first year of follow-up. Totals may not sum exactly because of rounding.

that about 4,600 multiple primaries were being recorded each year by 1981, and that this figure will increase by perhaps 200 a year for several more years. It would be expected to stabilize only when all prevalent cases of cancer have been diagnosed since 1971.

The multiple tumor data studied here originated as a spin-off from the acquisition of passive survival data by flagging of cancer patients at NHSCR. As such, the linkage of two tumors to one individual has been carried out without the detailed checks made by many individual registries with an interest in multiple primary malignancy. Whilst this carries disadvantages, such as the need to exclude administrative errors of registration, there is at least one compensation. It may be an advantage to hold multiple records which would be considered as multiple primary malignancy by some criteria, but not

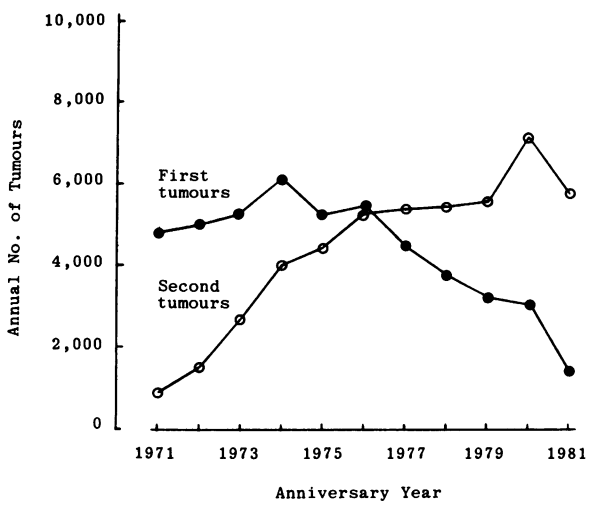

FIG. 5. Multiple primary tumors, England and Wales, 1971–81.

by others. The data do not depend on the past application of criteria which might now be considered inappropriate. New or alternative sets of criteria can be applied to the entire data set in order to demonstrate any differences in recorded incidence which their application would be likely to produce. Equally, but on a more parochial note, systematic examination of the errors of registration detected in this study will be expected to lead to improvements in the National Cancer Registration scheme.

Since flagging only began in 1971, any second cancers arising since then in individuals with a previous, unflagged cancer registered before 1971 will not have been linked to the prior tumor. The proportion of second cancers undetected for this reason will be expected to decay steadily, reaching zero when all surviving cancer patients have been registered since 1971, and flagged. For many cancers, survival beyond 10 or 12 years is still uncommon, and the OPCS multiple records may already be expected to contain virtually all second cancers that have been registered.

The overall risk of a second tumor is not raised, a result which is consistent with those recently reported from Finland [7] and Denmark [Storm et al., this issue], but at odds with results from Connecticut [Boice et al, this issue]. The downward trend of second cancer risk with time since diagnosis of the first tumor was unexpected and is opposite to the trends reported from all three registries mentioned above, although none of the trends is large. Possible explanations include under-registration of second cancer, particularly for patients diagnosed in the early 1970s when there may have been less awareness of multiple tumors, and less readiness to attach a new tumor diagnosis to the patient's record for ultimate abstraction by registry staff. The Danish study cited above has suggested that under-registration there may have resulted in up to 20 percent reduction in observed second-cancer risk. It is also possible that efficiency of linkage between two tumors at NHSCR has improved since flagging of tumor registrations began in 1971. Up to 14 percent of multiple primaries may also have been excluded from the data by the automatic editing processes described here. Inclusion of these records will require additional checks on the accuracy of the data. Finally, mortality data for cases registered in 1971 and 1972 is now known to have been complete only up to October 1981: the use of 31 December 1981 as the end of study date for these subjects will have resulted in overestimation of person-years at risk, and a corresponding reduction in risk (O/E) at 10+ and 9+ years, respectively.

Further analysis will now be done to explore links between specific pairs of primary sites, after refinement of the criteria used to distinguish multiple primaries from duplicate registrations. The OPCS data on multiple primary malignant neoplasms should be particularly valuable for the study of more recently introduced therapeutic regimes for a first primary cancer, because the large volume of data will enable precise risk estimation, to compensate in part for the relatively short duration of follow-up.

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