

Bladder cancer mortality in England and Wales in relation to cigarette smoking and saccharin consumption

BRUCE ARMSTRONG AND RICHARD DOLL

DHSS Cancer Epidemiology and Clinical Trials Unit and Department of the Regius Professor of Medicine, Radcliffe Infirmary, Oxford OX2 6HE

SUMMARY

Cohort analyses of bladder cancer mortality rates in men and women in England and Wales have been compared with figures for the per caput consumption of saccharin and cigarette tobacco and with similar analyses of cigarette smoking habits. The increase in bladder cancer mortality rates in male cohorts born since 1870 can be attributed to cigarette smoking, and there is no evidence of any break in the continuity of the trends in either men or women which corresponds to the introduction of saccharin.

INTRODUCTION

Sodium cyclamate was banned from use as an artificial sweetener in food in the United Kingdom (Minister of Agriculture, Fisheries and Food and Secretary of State for Social Services, 1969a and b) following a report of experiments in which a 10 : 1 mixture of cyclamate and sodium saccharin induced bladder cancer in rats (Price *et al.*, 1970). The possibility that saccharin may have been the carcinogen has since been considered. Saccharin and cholesterol pellets have induced cancer when implanted into the bladder of mice (Allen *et al.*, 1957) and saccharin, containing 810 ppm of o-toluene sulphonamide as an impurity, has enhanced the effect of methyl nitroso-urea in producing cancer of the bladder when fed to rats (Hicks, Wakefield, and Chowaniec, 1973). Unpublished studies have also been reported to show that bladder tumours were induced in rats by feeding saccharin as 5.7.5% of the diet (BIBRA Information Bulletin, 1973).

The above reports have aroused considerable concern, since a restriction on saccharin use might

mean that there would be no satisfactory non-caloric sweetener for use with calorie or carbohydrate restricted diets. We have therefore examined the trends in consumption of saccharin and the mortality from bladder cancer in England and Wales to see whether there is any epidemiological evidence that the two might be related. Since bladder cancer is known to be related to cigarette smoking (Cole, Monson, Haning, and Friedell, 1971), we have also compared trends in bladder cancer mortality with the consumption of cigarettes.

DATA AND METHODS

Bladder cancer mortality rates for men and women in England and Wales in five-year age groups for five-year periods from 1911-15 to 1961-65 were taken from published mortality tables (Case and Pearson, 1957; Case, Coghill and Harley, 1968) and rates for 1966-70 were calculated from the Registrar General's reports (Office of Population Censuses and Surveys, 1968-72).

Per caput saccharin consumption was calculated from data supplied by the sole British manufacturer of saccharin. These data were derived from records of total saccharin production dating back to 1939. The proportion of this production destined for human ingestion (about 80%) was estimated from accurate records available since 1969 and, before 1969, from some recorded facts and the recollections of current and retired staff members of the manufacturing company. No corrections could be made for saccharin exported by companies other than the manufacturing company, but it was considered that such exports would negligibly reduce the consumption figures given. Corrections for imports since 1960 were made from figures supplied by

H.M. Customs and Excise, assuming that a similar proportion of imported saccharin as locally produced saccharin was destined for human ingestion. Prior to 1960 saccharin imports were negligible due to high tariffs.

Per caput cigarette tobacco consumption and the percentage of current cigarette smokers among men and women were taken from the results of surveys reported by the Tobacco Research Council (Todd, 1972) for years since 1956. Figures for 1949 were taken from a report of Browne (1950).

Cohort analysis of mortality rates was carried out as described by Case (1956) except that mortality and year of birth were used as axes rather than mortality and age at death. This technique was recommended by Hoover and Cole (1971) and provides results which are, in our opinion, easier to interpret by inspection as it allows changes to be seen readily whether occurring with a particular cohort or in a particular five-year period.

A similar analysis was made of the percentage of current cigarette smokers. The data did not permit a quinary-quinquennial analysis, so the percentage of current cigarette smokers in each age-group was plotted against the median year of birth for that group, calculated from the year of the survey. For example, the age group 50-59 has a median age of 55 years, therefore the age group 50-59 in 1971 would have 1916 as its median year of birth. The 60 + years age group was assumed to have a median age of 70 years.

RESULTS

Bladder cancer mortality rates for men and women are shown in Tables I and II and Figures 1 and 2. Mortality in women (Table II and Fig. 2) shows a slow increase over the whole period which is more marked in the older groups. Mortality rates in men in the age groups from 50 to 74 years show a sharp increase which begins with the experience of cohorts born around 1875 and ends with the experience of cohorts born around 1900. Similar increases are seen in age groups from 75 to 84 years except that they begin with cohorts born 10 years earlier. In cohorts born subsequent to 1900, the mortality rates have been steady or have declined.

If the increase in bladder cancer mortality in the male cohorts born since 1870 (or 1860 in older groups) is real and the extra deaths are assumed to be due to the exposure of these cohorts to a new

carcinogenic agent in the environment, the number of deaths attributable to this agent in 1966-70 can be estimated very approximately by applying the age-specific rates of the 1870 cohort (Table I) to the mean population in 1966-70 (Office of Population Censuses and Surveys, 1968-72) and subtracting the number so calculated from the number observed. By this method the number of deaths attributable to the new agent in men aged 40-84 years in 1966-70 is estimated to be 12,048 minus 7,712, that is 4,336 or 36% of the number actually observed (12,048). A similar calculation gives a figure of 11% in women.

Per caput saccharin consumption is shown in Fig. 3 in arbitrary units, taking the consumption in 1939 equal to 1. Consumption rose sharply with sugar rationing at the beginning of the war and declined from 1948 to 1954. It rose again from 1955 onward, although at a decreased rate during the period of cyclamate use. The use in 1972 was about 8 g/person per year. Although quantitative data are not available for saccharin consumption before 1939, saccharin has been used since the late nineteenth century and there are some few individuals who have consumed it for over 50 years (Armstrong, to be published).

Cigarette tobacco consumption by sex is shown in Fig. 4, the percentage of current cigarette smokers by age and year of survey in men and women is shown in Table III, and the percentage of current cigarette smokers by age and birth cohort is shown in Figure 5. Figures from the 1949 survey (Browne, 1950) were plotted in Fig. 5 only for the oldest group which, in that survey, was 65 years +. The other data were not plotted because the age groups differed from those of the Tobacco Research Council surveys.

The cigarette consumption data are less complete than could be desired, but it is apparent that the percentage of current male smokers reached its peak with or before the cohort born around 1900 and has since declined. The peak in women was probably not reached until the cohorts of 1920 to 1925, since when it has remained fairly steady.

DISCUSSION

Examination of the trends in mortality from bladder cancer provides no evidence of any break in continuity that could be attributed to the use of saccharin since 1939. Any such break would be expected to have occurred within a particular five-year period rather than with a particular cohort as all age groups would have participated in the

TABLE I

MORTALITY (PER 1,000) FROM CANCER OF THE BLADDER 1911-70 IN ENGLAND AND WALES, MEN AGED 40-84 YEARS, WITH MEDIAN YEAR OF BIRTH INDICATED ON THE DIAGONALS

Age	Year of Birth												Year of Birth— <i>cont.</i>
	1830	1835	1840	1845	1850	1855	1860	1865	1870	1875	1880	1885	
80-84	0.387	0.386	0.454	0.471	0.549	0.588	0.592	0.737	0.976	1.095	1.244	1.379	
75-79	0.395	0.463	0.456	0.532	0.560	0.550	0.586	0.665	0.809	0.877	0.942	1.022	1890
70-74	0.344	0.400	0.361	0.398	0.431	0.432	0.443	0.494	0.587	0.624	0.690	0.727	1895
65-69	0.258	0.280	0.287	0.280	0.292	0.285	0.326	0.355	0.404	0.430	0.450	0.509	1900
60-64	0.177	0.177	0.184	0.182	0.183	0.204	0.220	0.239	0.269	0.265	0.285	0.278	1905
55-59	0.087	0.095	0.098	0.100	0.115	0.114	0.128	0.143	0.149	0.153	0.146	0.148	1910
50-54	0.054	0.049	0.048	0.062	0.062	0.060	0.079	0.075	0.086	0.069	0.071	0.070	1915
45-49	0.025	0.024	0.027	0.021	0.036	0.034	0.041	0.039	0.039	0.035	0.033	0.033	1920
40-44	0.013	0.011	0.012	0.012	0.013	0.015	0.012	0.017	0.014	0.016	0.014	0.012	1925
	1911 -15	1916 -20	1921 -25	1926 -30	1931 -35	1936 -40	1941 -45	1946 -50	1951 -55	1956 -60	1961 -65	1966 -70	
	Year of Death												

TABLE II

MORTALITY (PER 1,000) FROM CANCER OF THE BLADDER 1911-70 IN ENGLAND AND WALES, WOMEN AGED 50-84 YEARS, WITH MEDIAN YEAR OF BIRTH INDICATED ON THE DIAGONALS

Age	Year of Birth												Year of Birth— <i>cont.</i>
	1830	1835	1840	1845	1850	1855	1860	1865	1870	1875	1880	1885	
80-84	0.135	0.137	0.211	0.184	0.218	0.221	0.224	0.286	0.349	0.364	0.349	0.397	
75-79	0.153	0.131	0.156	0.188	0.186	0.201	0.223	0.239	0.266	0.267	0.267	0.276	1890
70-74	0.116	0.117	0.116	0.135	0.150	0.154	0.146	0.174	0.169	0.174	0.172	0.179	1895
65-69	0.078	0.080	0.098	0.106	0.094	0.106	0.107	0.120	0.111	0.119	0.108	0.114	1900
60-64	0.056	0.058	0.067	0.061	0.059	0.068	0.075	0.074	0.065	0.068	0.066	0.067	1905
55-59	0.035	0.034	0.038	0.036	0.037	0.040	0.041	0.040	0.043	0.039	0.041	0.041	1910
50-54	0.019	0.020	0.022	0.022	0.018	0.023	0.027	0.026	0.025	0.021	0.023	0.020	1915
	1911 -15	1916 -20	1921 -25	1926 -30	1931 -35	1936 -40	1941 -45	1946 -50	1951 -55	1956 -60	1961 -65	1966 -70	
	Year of Death												

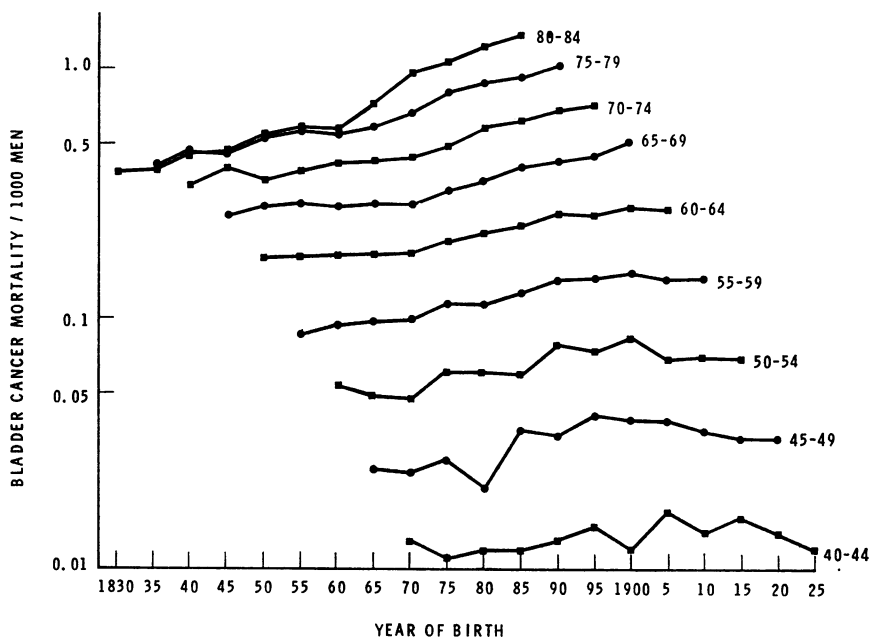


FIG. 1. Mortality from bladder cancer in men in England and Wales plotted in five-year age groups by median year of birth.

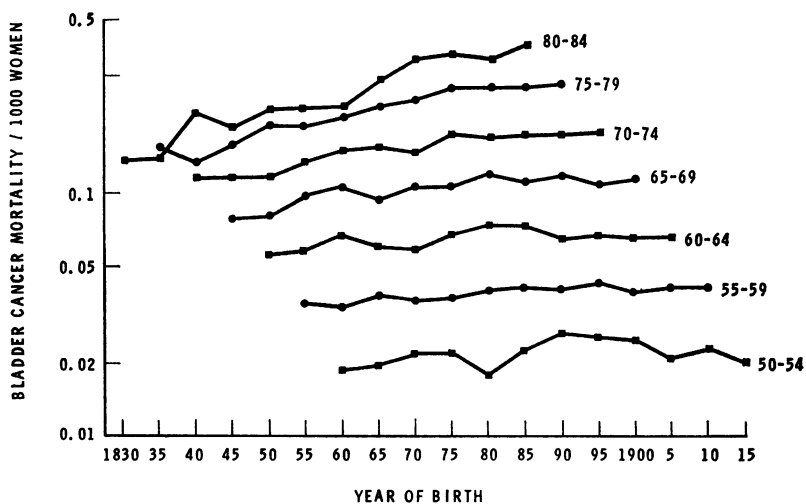


FIG. 2. Mortality from bladder cancer in women in England and Wales plotted in five-year age groups by median year of birth.

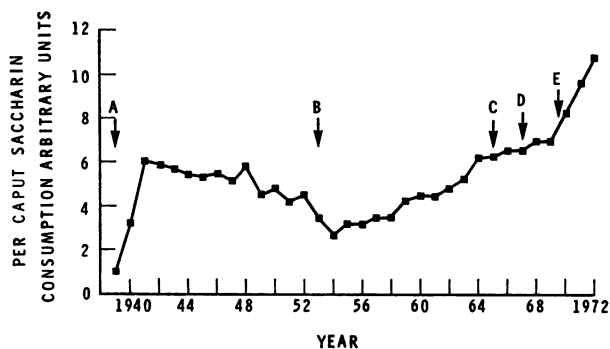


FIG. 3. Per caput saccharin consumption in the United Kingdom from 1939 to 1972 (A = beginning of second world war; B = termination of sugar rationing; C = cyclamate permitted in soft drinks; D = cyclamate permitted in sweetening tablets; E = cyclamate banned.)

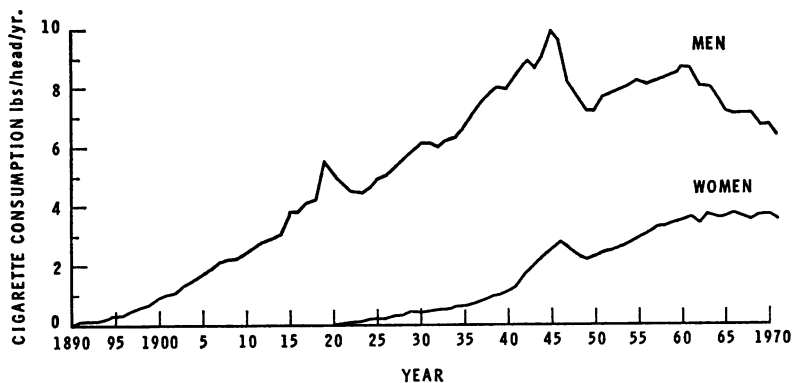


FIG. 4. Per caput cigarette tobacco consumption in men and women in the United Kingdom from 1890 to 1971.

TABLE III
PERCENTAGE OF CURRENT CIGARETTE SMOKERS, MEN AND WOMEN, IN UNITED KINGDOM SURVEYS, 1956-71*

	Age	Year of Survey								
		1956	1958	1961	1963	1965	1968	1969	1970	1971
Men	20-24	66	65	70	68	66	62	65	63	60
	25-34	72	66	67	67	63	60	63	63	60
	35-49	74	72	72	66	64	64	63	61	58
	50-59	74	72	69	66	65	65	65	62	56
	60+	56	53	56	51	56	56	54	55	51
Women	20-24	44	45	52	50	51	53	53	54	50
	25-34	52	48	51	49	50	48	54	51	49
	35-49	48	50	54	56	54	54	55	52	51
	50-59	37	38	42	44	46	48	44	48	46
	60+	29	19	24	24	23	24	25	26	24

*Taken from Todd (1972) Table 6, with corrections made for the percentage of pipe only and cigar only smokers in men. Figures for 1949 omitted, see text.

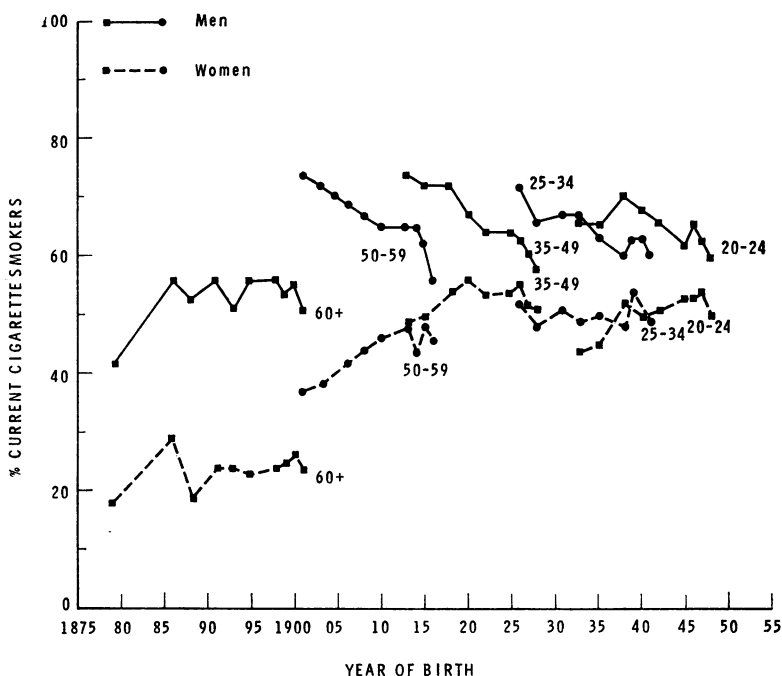


FIG. 5. Percentage of current cigarette smokers in men and women in various age groups in the United Kingdom, plotted by median year of birth.

increased saccharin consumption during and subsequent to the second world war. In Tables I and II there are no increases in bladder cancer rates affecting all age groups since 1941. Whereas the rates in older groups are increasing, the rates in younger groups are either stable or decreasing.

The trends seen in bladder cancer mortality in men are compatible, however, with the idea that the increases may be attributed to cigarette smoking. This is supported by the correspondence between the first male cohorts to show a sharp increase in bladder cancer mortality (those born from around 1865 to around 1875) and the beginning of significant cigarette smoking by men (1890, when these cohorts would have had mean ages of 15-25 years); and by the correspondence between the male cohort with peak bladder cancer mortality (that born around 1900) and that with the maximum percentage of cigarette smokers.

In women, there are no clear increases in bladder cancer mortality corresponding to the mass increase in cigarette consumption starting in 1920. From the pattern seen in men, an increase might have been expected in cohorts born from 1895 to 1905 (i.e., 15 to 25 years before the increase in cigarette consumption). The absence of a cohort pattern of

increase in these rates may be due to the relatively slow initial increase in cigarette tobacco consumption from 1920 to 1940 (Fig. 4), followed by widespread adoption of the habit by women of all ages between 1940 and 1946. There are no data on the increase in cigarette consumption by age in women during the second world war; but it seems likely that it affected women over a broad range of ages at the same time, rather than a specific cohort. The absence of a clearly identifiable cross-sectional rise in bladder cancer mortality in women since the war may be due to the relatively weak carcinogenic effect of tobacco smoke on the bladder (Doll, 1972) and the comparatively short period which has elapsed (25 years to 1970).

The estimated mortality from bladder cancer in men attributable to a 'new' agent (36%) is similar to that attributed to cigarette smoking in retrospective and prospective studies (52%, Doll, 1972; 39%, Cole *et al.*, 1971). The figure of 11% in women obtained by the same method is somewhat less than that found in studies on individuals (29%, Cole *et al.*, 1971) but is consistent with the belief that cigarette smoking has contributed to the incidence of bladder cancer in women. Both estimates might be expected to be lower than

other estimates of the percentage of bladder cancer risk attributable to cigarette smoking as, in both sexes, cohorts born earlier than 1875 must have been affected to some extent by cigarette smoking.

The absence of an increase in bladder cancer mortality which might be attributed to saccharin consumption is reassuring, but the following considerations make this evidence far from conclusive:

(1) If the minimum time necessary to see significant numbers of bladder cancers induced by saccharin were more than 30 years (allowing for five years from induction to death) it would be too early to see an effect of saccharin consumption on mortality rates. No reasonable a priori assumption can be made of induction time for saccharin carcinogenesis. The mean induction time for occupational bladder cancers in the dye industry was 18 years, but some occurred as early as two years after exposure (Case, Hosker, McDonald, and Pearson, 1954). By contrast, bladder cancer as a result of cigarette smoking is probably rare under 20 years from commencement of the habit as mortality rates in men under 40 years of age have remained unchanged over the period of adoption of cigarette smoking.

(2) The mean consumption of saccharin at the 1972 level was about 0.3 mg/kg/day for a 70 kg man; whereas the amount that produced bladder cancers in rats was about 2.5 g/kg/day, that is 8,300 times as much. Saccharin consumption is, of course, not evenly distributed, but there can be few men who consume even one five-hundredth of the effective dose (weight for weight) in rats; that is, 28 tablets a day.

(3) With the widespread use of saccharin in soft drinks, most of the population are probably exposed to small quantities. Only about 14% of the adult population are regularly exposed to larger amounts as sweetening tablets or calorie-reduced foods (Armstrong, to be published). This relatively small proportion would have to experience a substantial increase in the risk of bladder cancer before an effect could be detected in the figures for the population as a whole.

There is clearly no epidemic of bladder cancer in England and Wales as a result of saccharin consumption. It will, however, not be possible to say whether people exposed to large amounts of saccharin are at increased risk of developing bladder cancer until we have the results of detailed observations on individuals.

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