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SMOKING AND CANCER MORTALITY AMONG U.S. VETERANS: A 26-YEAR FOLLOW-UP

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On the 30th anniversary of the U.S. Surgeon General's report *Smoking and Health,* we present updated results from one of the original cohort studies that comprised the groundbreaking document. A 26-year follow-up of 248,046 U.S. veterans evaluating the risks of cigarette smoking revealed strong dose–response effects between smoking and total cancer and a large number of cancer sites. Over 50% of cancer deaths among current smokers and 23% of cancer deaths among former smokers were attributable to cigarette smoking. These findings further demonstrate the large and unique role cigarette smoking plays in cancer etiology and the importance of smoking cessation to reduce this enormous public health burden.

Thirty years ago, the first report by the U.S. Surgeon General (1964) on smoking and health was published. The epidemiological evidence was obtained in part from the initial follow-up of a large cohort study of U.S. veterans, initiated at the National Cancer Institute in 1953 (Dorn, 1958, 1959) and from 6 other prospective surveys of mortality among groups of smokers. Herein we report an extended follow-up of the veterans cohort, evaluating cancer deaths by cause over a 26-year span, during which time most of the subjects had died and over 3,000,000 person–years of observation accumulated. In earlier reports of the extended follow-up we have presented smoking-related risks for selected cancer sites (McLaughlin *et al.,* 1989, 1990*a,b;* Hsing *et al.,* 1990, 1991; Heineman *et al.,* 1992, 1994; Chow *et al.,* 1993), but this report is the first relating cigarette smoking to the long-term risks of all forms of cancer in this cohort.

MATERIAL AND METHODS

Subjects were U.S. veterans who held government life insurance policies active at the end of 1953. They were 31 to 84 years old at the start of follow-up, most having served during World War I, though some entered service subsequently. Less than 0.5% were women, and an even smaller percentage were non-white men. The methods of data collection and of earlier mortality follow-up have been described in detail elsewhere (Rogot and Murray, 1980). In brief, a questionnaire requesting information about the use of tobacco, residence, usual occupation, and industry of employment was mailed to policyholders early in 1954. Usable replies were obtained from 68% of the subjects. After a subsequent mailing early in 1957 to non-respondents of the first mailing, 248,046 (84%) policyholders responded.

Based on the questionnaire responses, we grouped individuals into the following tobacco smoking categories: (1) non-smokers: never smoked cigarettes, cigars or pipe regularly (n = 55,049); (2) former cigarette smokers: regularly smoked cigarettes in the past but smoked no tobacco products at the time of the questionnaire (n = 40,734); and (3) regular current (at the time of the questionnaire) cigarette smokers: currently regularly smoked cigarettes but not cigars or pipes, though may have smoked cigars or pipes in the past (n = 82,120). Current smokers were also subdivided into 4 cigarettes/day groups (1–9: n = 8,908; 10–20: n = 41,293; 21–39: n = 37,232; and 40^+ cigarettes/day: n = 4,687). Excluded from our analysis were current regular cigar and pipe smokers who did not currently regularly smoke cigarettes (n = 34,219), as well as those with other or mixed types of smoking or amount of cigarette smoking unknown (n = 35,924).

Mortality among cohort members through September 30, 1980 was ascertained by means of the Beneficiary Identification and Records Locator Subsystem (BIRLS) of the Veterans Administration (VA). BIRLS records the fact of death from death notices received by the VA in connection with claims for burial benefits of veterans, regardless of their insurance status. Deaths among veterans of World War I with more than 15 days' service, and thus eligible for VA benefits, can be identified through the VA for 96% of those deceased (Beebe and Simon, 1969), a level of completeness recently verified by matching a systematic sample of 1,000 subjects against the mortality files maintained by the Social Security Administration (J. Vaught, personal communication). Through BIRLS it has been possible to determine mortality even for those veterans whose insurance policies had lapsed.

Causes of death were obtained from VA claims folders or from copies of death certificates sought from the states where the deaths occurred. Underlying and contributory causes were coded by trained nosologists according to the International Statistical Classification of Diseases (ICD) (World Health Organization, 1957). The 7th revision was used to maintain consistency with previous coding. An underlying cause of death was coded for 95% of deaths.

Person–years of follow-up were accumulated from the year of the questionnaire response, January 1, 1954 or 1957, to the date of death or to September 30, 1980 for those then alive. The 181 subjects with unknown year of death were retained until the cut-off date.

Relative risks (RRs) of total and site-specific cancer mortality in the several smoking groups compared to never-smokers were computed by fitting Poisson regression models with maximum likelihood methods (Breslow and Day, 1987). The RR analyses were adjusted for attained age and for calendar year time period, each in 5-year groupings, and score tests of significance of trends were carried out (Preston *et al.,* 1990). Attributable risks or proportion of cancer deaths among smokers due to smoking were calculated using standard methods (Breslow and Day, 1987).

RESULTS

Among the 177,903 non-, former, and current smokers in this report, 3,252,983 person–years accumulated and 116,606 (66% of the cohort) deaths occurred in the 26-year follow-up period. Death rates for all causes were 70% higher for current cigarette smokers (RR = 1.7; 95% CI = 1.67, 1.72) and 20% higher for former smokers (RR = 1.2; 95% CI = 1.18, 1.22) than for non-smokers.

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TABLE I – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) OF CANCER MORTALITY 1954–1980 AMONG CURRENT AND FORMER CIGARETTE SMOKERS AT START OF FOLLOW-UP

Site of cancer	Number of deaths	Ever smoked		Former		Current	
		RR	95% CI	RR	95% CI	RR	95% CI
All sites	21,676	1.8	(1.7, 1.8)	1.3	(1.3, 1.4)	2.1	(2.0, 2.2)
Oral	189	2.6	(1.8, 3.9)	1.5	(0.9, 2.4)	3.4	(2.3, 5.0)
Pharynx	143	9.5	(4.6, 19.4)	2.6	(1.1, 6.2)	14.1	(6.9, 28.9)
Esophagus	318	3.0	(2.3, 4.1)	1.5	(1.0, 2.2)	4.1	(3.0, 5.6)
Stomach	1,058	1.3	(1.1, 1.4)	1.0	(0.9, 1.2)	1.4	(1.2, 1.6)
Colon	2,596	1.3	(1.2, 1.4)	1.4	(1.2, 1.5)	1.2	(1.1, 1.4)
Rectum	735	1.4	(1.2, 1.6)	1.3	(1.0, 1.5)	1.4	(1.2, 1.7)
Liver	363	1.7	(1.3, 2.2)	1.5	(1.2, 2.0)	1.8	(1.4, 2.3)
Pancreas	1,264	1.4	(1.3, 1.6)	1.1	(0.9, 1.3)	1.7	(1.5, 1.9)
Larynx	167	10.2	(5.2, 20.0)	5.0	(2.4, 10.5)	13.7	(7.0, 27.1)
Lung	5,097	8.4	(7.5, 9.4)	3.6	(3.1, 4.1)	11.6	(10.4, 13.0)
Prostate	3,124	1.1	(1.1, 1.2)	1.1	(1.0, 1.2)	1.2	(1.1, 1.3)
Kidney	511	1.4	(1.1, 1.6)	1.1	(0.9, 1.4)	1.5	(1.2, 1.9)
Bladder	996	1.9	(1.6, 2.1)	1.3	(1.1, 1.6)	2.2	(1.9, 2.6)
Skin	282	1.2	(0.9, 1.5)	1.1	(0.8, 1.5)	1.3	(1.0, 1.6)
Brain	468	1.1	(0.9, 1.3)	1.1	(0.9, 1.4)	1.1	(0.9, 1.3)
Non-Hodgkin's lymphoma	638	1.0	(0.9, 1.2)	1.0	(0.8, 1.2)	1.0	(0.9, 1.2)
Hodgkin's disease	176	1.3	(0.9, 1.8)	0.9	(0.6, 1.3)	1.5	(1.1, 2.1)
Multiple myeloma	389	1.0	(0.8, 1.2)	1.0	(0.8, 1.3)	0.9	(0.7, 1.2)
Leukemia	1,132	1.3	(1.2, 1.5)	1.3	(1.1, 1.5)	1.3	(1.2, 1.5)

Table I shows RRs of total and site-specific cancer mortality. Current cigarette smokers had approximately twice the cancer risk of non-smokers (RR = 2.1; 95% CI = 2.0, 2.2), while the RR for former smokers was 1.3 (95% CI = 1.3, 1.4). In total, 21,676 cancer deaths were recorded, 11,515 among current and 4,734 among former smokers and 5,427 among non-smokers. Based on calculations of attributable risk among the exposed, 52% of all cancer deaths among current smokers and 23% of all cancer deaths among former smokers were due to cigarette smoking.

Significantly elevated risks among current smokers were found for 15 of the 19 types of cancer evaluated (Table I). The 4 exceptions were skin and brain cancers, non-Hodgkin's lymphoma and multiple myeloma. Among former smokers, significant increases were found for 9 cancer sites. For cancers of the oral cavity, esophagus, stomach, pancreas and kidney and for Hodgkin's disease, plus the four cancers mentioned above, the risks in former smokers were not significantly different from those of non-smokers.

Table II shows RRs of cancer mortality for the periods 1954–1969 *vs.* 1970–1980. Elevated RRs among current cigarette smokers were essentially unchanged over the successive follow-ups for all cancer and for cancers of the pharynx, pancreas, lung and bladder. RRs increased to some degree in 1970–1980 for cancers of the colon, rectum and larynx and decreased rather substantially for cancers of the oral cavity, esophagus, stomach and liver and for Hodgkin's disease and leukemia.

Table III shows risks of cancer death among current smokers, relative to non-smokers, according to numbers of cigarettes usually smoked per day. For all cancers combined and for 15 of the 19 cancer sites, there were significant trends of rising risk with increasing intensity of smoking.

TABLE II – RELATIVE RISKS AND 95% CONFIDENCE INTERVALS OF CANCER MORTALITY DURING 1954–1969 AND 1970–1980 AMONG CURRENT SMOKERS

Site of cancer	1954–1969	1970–1980
All sites	2.2 (2.1, 2.3)	2.0 (1.9, 2.1)
Oral	4.3 (2.6, 7.0)	2.2 (1.1, 4.1)
Pharynx	14.4 (5.8, 35.7)	13.4 (4.1, 43.6)
Esophagus	6.3 (3.9, 10.1)	2.6 (1.7, 4.0)
Stomach	1.5 (1.3, 1.8)	1.2 (1.0, 1.5)
Colon	1.1 (1.0, 1.3)	1.4 (1.2, 1.6)
Rectum	1.2 (1.0, 1.5)	2.0 (1.5, 2.8)
Liver	2.2 (1.6, 3.1)	1.2 (0.8, 1.9)
Pancreas	1.7 (1.5, 2.1)	1.6 (1.3, 1.9)
Larynx	11.9 (5.2, 27.2)	17.8 (5.5, 57.5)
Lung	11.7 (10.1, 13.7)	11.6 (9.7, 13.7)
Prostate	1.3 (1.1, 1.5)	1.1 (1.0, 1.2)
Kidney	1.4 (1.1, 1.9)	1.7 (1.2, 2.3)
Bladder	2.2 (1.8, 2.7)	2.3 (1.8, 2.8)
Skin	1.4 (0.9, 2.1)	1.1 (0.8, 1.7)
Brain	1.1 (0.9, 1.4)	1.0 (0.7, 1.5)
Non-Hodgkin's lymphoma	1.1 (0.9, 1.4)	0.9 (0.6, 1.2)
Hodgkin's disease	1.8 (1.2, 2.7)	0.9 (0.4, 1.7)
Multiple myeloma	0.8 (0.6, 1.1)	1.2 (0.8, 1.7)
Leukemia	1.6 (1.3, 1.9)	1.1 (0.9, 1.3)

DISCUSSION

This long-term follow-up of a large cohort of American veterans shows a continuing excess mortality related to smoking. The higher the frequency of cigarette use reported in the 1950s, the greater the risk of death over the next 26 years for all cancers combined and for various cancer sites. The tendency for risks to diminish with time was generally slight and apparent only for certain cancers.

Changes in smoking habits by the participants since the time of the questionnaire have not been determined. Because all of the respondents were over 30 years old, it can reasonably be assumed that among those who never smoked in the 1950s, not many would have started smoking subsequently. Furthermore, although some former smokers may have resumed smoking, the percentage may be small since 61% of those reporting cessation indicated they had stopped smoking 5 or more years prior to the questionnaire administration. It is likely, however, that a sizable fraction of current 1954/1957 smokers stopped smoking prior to the end of follow-up. Veterans tended to have higher levels of education and income than their civilian counterparts (Hammond, 1980), attributes associated with increased rates of smoking cessation (Kabat and Wynder, 1987). Therefore, smoking cessation among veterans during the follow-up period probably was at least as great as that among all U.S. men in the corresponding year-of-birth cohorts. The prevalence of current smokers among adult men in the United States declined considerably over the follow-up period,

TABLE III - RELATIVE RISKS AND 95% CONFIDENCE INTERVALS OF CANCER MORTALITY 1954–1980 AMONG CURRENT SMOKERS AT START OF FOLLOW-UP ACCORDING TO NUMBER OF CIGARETTES SMOKED PER DAY

Site of cancer	Cigarettes per day				*p* for trend
	1–9	10–20	31–39	40+	
All sites	1.3 (1.2, 1.4)	1.9 (1.9, 20)	2.6 (2.5, 2.7)	3.2 (3.0, 3.4)	<0.01
Oral	0.6 (0.2, 2.1)	2.5 (1.6, 4.0)	5.4 (3.5, 8.4)	8.6 (4.7, 15.7)	<0.01
Pharynx	5.2 (1.8, 15.0)	12.6 (6.0, 26.6)	18.1 (8.5, 38.7)	37.3 (15.9, 87.5)	<0.01
Esophagus	1.4 (0.7, 2.7)	3.3 (2.4, 4.7)	6.7 (4.7, 9.4)	6.1 (3.5, 10.7)	<0.01
Stomach	1.3 (1.0, 1.7)	1.4 (1.2, 1.6)	1.4 (1.2, 1.8)	1.9 (1.3, 2.7)	<0.01
Colon	1.1 (0.9, 1.3)	1.2 (1.1, 1.4)	1.3 (1.1, 1.5)	1.7 (1.3, 2.1)	<0.01
Rectum	1.3 (1.0, 1.9)	1.3 (1.1, 1.6)	1.6 (1.2, 2.0)	1.5 (0.9, 2.4)	<0.01
Liver	1.8 (1.1, 2.8)	1.4 (1.1, 2.0)	2.3 (1.6, 3.1)	2.6 (1.4, 4.6)	<0.01
Pancreas	1.4 (1.1, 1.8)	1.7 (1.4, 1.9)	1.8 (1.5, 2.2)	1.6 (1.1, 2.3)	<0.01
Larynx	4.7 (1.7, 13.3)	11.2 (5.5, 22.8)	18.3 (8.9, 37.4)	45.1 (20.6, 99.0)	<0.01
Lung	3.7 (3.1, 4.5)	9.9 (8.8, 11.2)	16.9 (15.0, 19.0)	22.9 (19.8, 26.6)	<0.01
Prostate	1.0 (0.9, 1.2)	1.1 (1.0, 1.3)	1.2 (1.1, 1.4)	1.6 (1.2, 2.0)	<0.01
Kidney	1.3 (0.9, 2.0)	1.4 (1.1, 1.8)	1.6 (1.3, 2.2)	2.2 (1.4, 3.5)	<0.01
Bladder	1.1 (0.8, 1.5)	2.3 (1.9, 2.7)	2.7 (2.2, 3.3)	2.2 (1.5, 3.3)	<0.01
Skin	1.6 (1.0, 2.6)	1.3 (1.0, 1.8)	1.1 (0.7, 1.6)	0.6 (0.2, 1.9)	0.93
Brain	1.3 (0.9, 1.9)	1.1 (0.8, 1.4)	1.1 (0.8, 1.4)	0.7 (0.3, 1.5)	0.87
Non-Hodgkin's lymphoma	1.1 (0.8, 1.6)	1.0 (0.8, 1.2)	1.0 (0.8, 1.3)	1.2 (0.7, 2.0)	0.49
Hodgkin's disease	1.8 (1.0, 3.3)	1.2 (0.8, 1.8)	1.9 (1.2, 2.9)	1.8 (0.8, 4.1)	0.01
Multiple myeloma	1.0 (0.6, 1.5)	1.0 (0.8, 1.3)	0.9 (0.6, 1.3)	0.6 (0.3, 1.5)	0.36
Leukemia	1.1 (0.8, 1.4)	1.4 (1.2, 1.6)	1.4 (1.1, 1.7)	1.2 (0.8, 1.9)	<0.01

from approximately 54% in the mid-1950s to around 38% by 1980 (Haenszel *et al.*, 1956; U.S. Surgeon General, 1989). Thus the persistence of the excess cancer risks among veterans who were current smokers in 1954/1957 is even more remarkable.

For all types of cancer combined, death rates were about twice as high during the 26-year follow-up among men who were current smokers in the 1950s compared to non-smokers and were elevated by 30% among men who had quit. The attributable risks among smokers, *i.e.*, the proportion of all cancers among smokers due to smoking, were high, namely over 50% for current smokers and 23% for former smokers. These large percentages indicate that cigarette smoking is a principal cause of cancer throughout adulthood among smokers. For some cancers, such as those of the pharynx, larynx and lung, smoking is the dominant cause of cancer death.

The long-term risks for most cancers were lower among those who had quit *vs.* continued smoking as of entry to follow-up, providing evidence that the effects of smoking are at least partly reversible. For cancers of the oral cavity, pharynx, esophagus, stomach, pancreas, larynx, lung, kidney and bladder, risks were markedly lower among former than current smokers. Other studies of these cancers assessing lifetime tobacco use tend to confirm these observations (U.S. Surgeon General, 1989) and suggest that for some tumors the risk falls rather quickly following smoking cessation. In a large (over 1,000 cases) case-control study in 4 U.S. metropolitan areas, for example, the risk of oral and pharyngeal cancer among smokers approached that of non-smokers within 10 years of quitting (Blot *et al.*, 1988). Similarly, risks of both bladder and kidney cancer declined sharply within a few years of smoking cessation (Hartge *et al.*, 1987; McLaughlin *et al.*, 1984). For lung cancer, the major smoking-induced cancer, the decline in risk appears to be more gradual, with long-term quitters still experiencing some elevation in risk compared to never smokers (U.S. Surgeon General, 1982).

Although we could not adjust for the potentially confounding effects of factors such as diet, alcohol or occupation, there was evidence that the alcohol intake of this cohort of veterans was not in excess. Compared with U.S. white males, the standardized mortality ratio (SMR) for cirrhosis of the liver was 53 (55% CI = 50–56), significantly below the national experience (Hsing *et al.*, 1990). SMRs for alcohol-related cancer sites, such as oral cavity, larynx and esophagus, were 53 (95% CI = 48–57), 43 (95% CI = 37–49) and 57 (95% CI = 52–62), respectively, indicating that these veterans had significantly fewer alcohol-related cancer deaths than U.S. white males during the study period.

The large size of the veterans cohort resulted in high precision in relative risk estimates. For all cancers combined and for each of the major cancers, 95% CIs for current and

former smokers and for each level of smoking were very narrow. Thus, for example, the 3.2-fold increase in risk of cancer death for heavy (40^+ cigarettes/day) smokers likely is quite precise (95% CI = 3.0–3.4). The narrow CIs also indicate that the increases in risk with increasing amount smoked per day are nearly linear for all cancers combined, lung cancer and several other sites.

Our extended analysis indicates that not all cancers are tobacco-related. Little or no differences in risk between smokers and non-smokers were detected for skin and brain cancers, lymphomas and multiple myeloma. Risks of these cancers (except lymphoma) actually tended to decrease with increasing amount smoked, but the trends were not statistically significant. The veterans data also provide evidence of modest but significant trends between smoking and the risks of stomach and colorectal cancers. Smoking has been inconsistently related to stomach cancer (McLaughlin *et al.*, 1990*a*) and only recently linked to colorectal cancer in long-term follow-ups (Giovannucci *et al.*, 1994*a,b;* Heineman *et al.*, 1994). For both cancers the risk increased as intensity of smoking increased. The overall RR of colon and rectum cancers among men reporting as current smokers in 1954/1957 was higher in 1970–1980 than in 1954–1969 and (for colon cancer) higher in former than in current smokers. These findings support the notion of an unusually long latency period for smoking-related cancers of the large bowel (Giovannucci *et al.*, 1994*a,b;* Heineman *et al.*, 1994). In the extended follow-up, risks of prostate and liver cancer and leukemia were slightly elevated among current smokers (Hsing *et al.*, 1990, 1991; McLaughlin *et al.*, 1989), but the increases were less evident in the more recent period.

In summary, the findings from this long-term prospective study of a large group of American men confirm that the increased cancer risks from smoking persist throughout much of adult life. The study provides some of the most precise estimates of the long-term carcinogenic effects of smoking. Smoking accounted for nearly half of all cancers during 1954–1980 among men who reported at the start of follow-up that they currently smoked cigarettes but less than one-fourth of all cancers among men who had quit smoking. The site-specific cancer risks associated with smoking are consistent with the pattern of smoking-related cancers reported in the literature. The data further confirm that the key to cancer prevention is cessation of smoking and call for expanded efforts to advise all smokers to quit and to urge young people not to start smoking.

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