

Confounding effects of lifestyle-related factors on cancer risk from low-dose radiation

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Epidemiological studies on cancer morbidity/mortality from low-dose radiation sometimes produce apparently statistically significant findings. The degrees of significance, however, are often quite low, and the results are possibly confounded by effects, such as lifestyle-related factors, which may have a strong impact on cancer morbidity/mortality and thus result in false-positives. Here, we discuss these possibilities in the light of the results of the Phase II Epidemiological Survey on Low-Dose Exposure of Radiation Workers.

1. Epidemiological Survey on Low-Dose Radiation Exposure

(<http://www.rea.or.jp/ekigaku/report2.pdf>) (Japanese)

Results of the Phase II Epidemiological Survey on Low-Dose Exposure of Radiation Workers showed statistically significant associations between increasing rates of mortality from cancer of the oesophagus, stomach, and rectum and increasing cumulative radiation doses.

However, lifestyle-related factors may have a stronger influence on the occurrence of cancer than radiation.

2. Causes of Cancer

In one study conducted on cancer causes in the US, tobacco and adult diet/obesity were the two biggest single risk factors identified (30% each). Various other risk factors are shown in the figure below. It is therefore necessary to demonstrate that the cancer observed in low-dose radiation studies was not caused by cigarette smoking or adult diet/obesity. Research should be carried out by deliberately controlling for factors other than radiation, as the incidence of cancer possibly caused by low-dose radiation is expected to be quite low. Results of similar studies on Japanese populations have not been published.

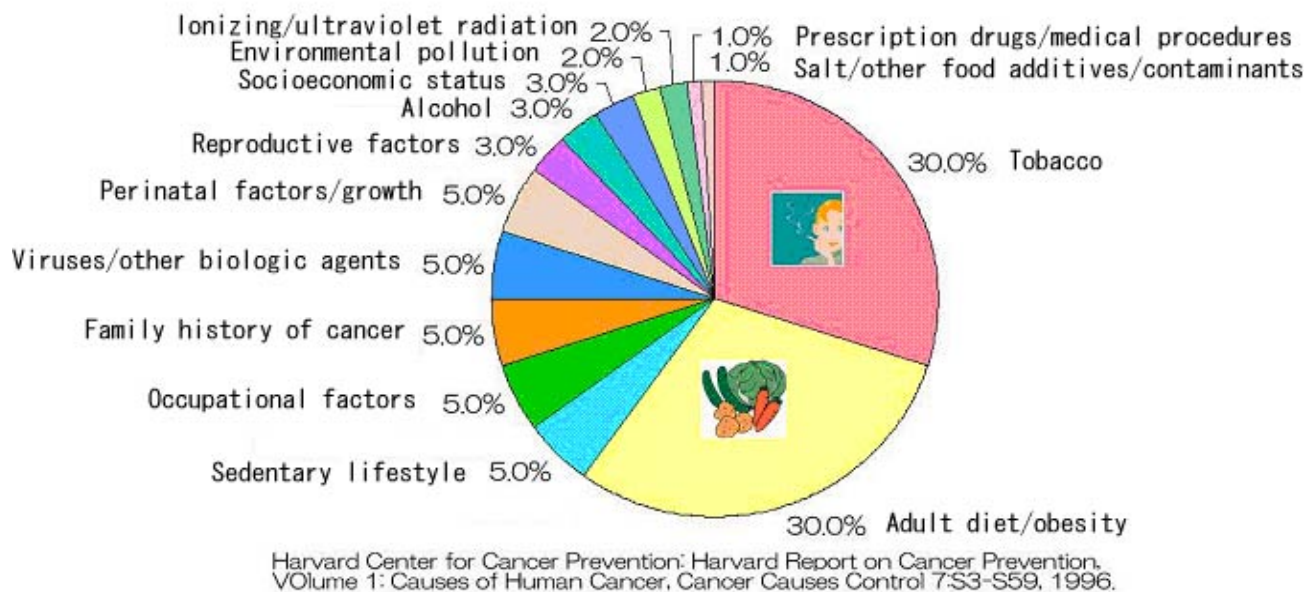


Fig. 1: Causes of cancer in the United States

3. Results of the Study on Effects of Lifestyle

(<http://www.rea.or.jp/ekigaku/report2cf.pdf>) (Japanese)

In conjunction with the Phase II Epidemiological Survey on Low-Dose Exposure of Radiation Workers, a separate analysis on lifestyle-related confounding factors was carried out on part of the study cohort. This showed that "larger cumulative radiation doses are associated with larger numbers of packs of cigarettes smoked, increased daily alcohol consumption, and the numbers of workers ever engaged in harmful operations; while they are inversely related to the percentages of workers ever having undergone stomach cancer screening tests." These associations were statistically significant. Detailed results on cigarette smoking and alcohol consumption are illustrated below:

(1) Association of cigarette smoking with cumulative radiation doses

Workers with higher cumulative doses clearly smoked higher total amounts of cigarettes.

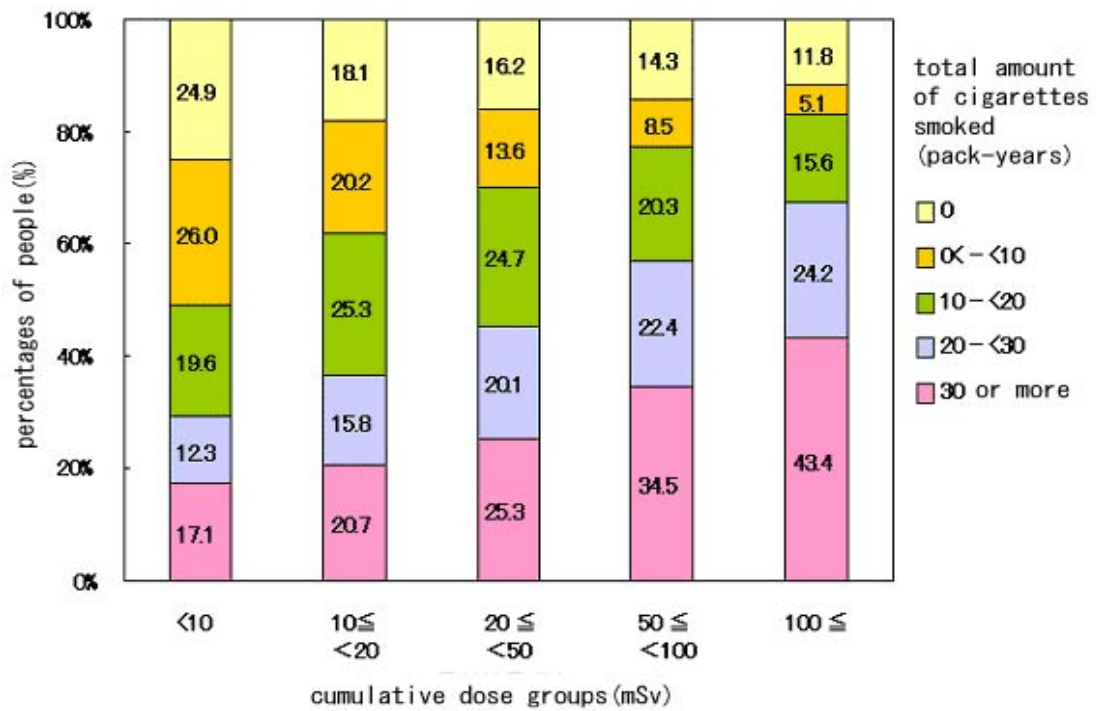


Fig. 2: Association of cigarette smoking with cumulative radiation doses

(2) Association of alcohol consumption with cumulative doses

Workers with higher cumulative doses showed a tendency to have increased daily alcohol consumption.

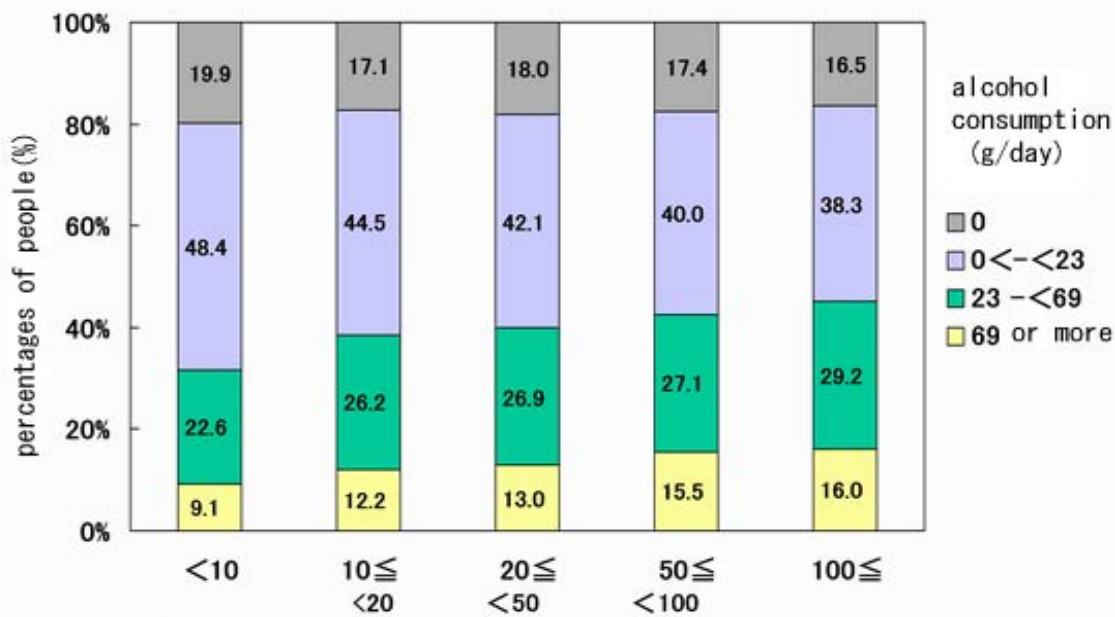


Fig. 3: Association of alcohol consumption with cumulative doses

4. Relationships between Lifestyle (smoking, drinking, etc.) and Cancer

Data concerning excess risks due to cigarette smoking, alcohol drinking and the like are derived from the Japan Public Health Center-based Prospective Study (<http://epi.ncc.go.jp/jphc/outcome/index.html>) (Japanese)

(1) Relationships between cigarette smoking and cancer

(<http://epi.ncc.go.jp/jphc/outcome/02/kit.html>) (Japanese)

Smoking index (pack-years: number of 20-cigarette packs smoked per day multiplied by the number of smoking years) used as a measure of the total amount of cigarettes smoked indicated that higher indices are associated with increased mortality rates from all causes, including cancers and cardiovascular disease.

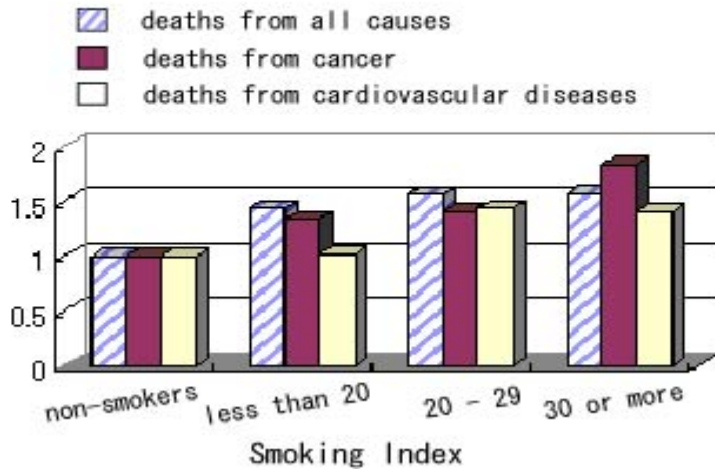


Fig.4: Relationships between amounts of cigarettes smoked and mortality rates - in men

(2) Relationships between alcohol drinking and cancer

(<http://epi.ncc.go.jp/jphc/outcome/01/inshu3.html>) (Japanese)

The study population was divided into 6 sub-groups depending on the amount drunk. Analysis of risks relative to unity for the sub-group of non-drinkers demonstrated that those with an average two-day intake of 180ml had the least relative mortality risk from all causes including cancers, while all the remaining sub-groups with greater or lesser alcohol consumption had higher relative mortality rates.

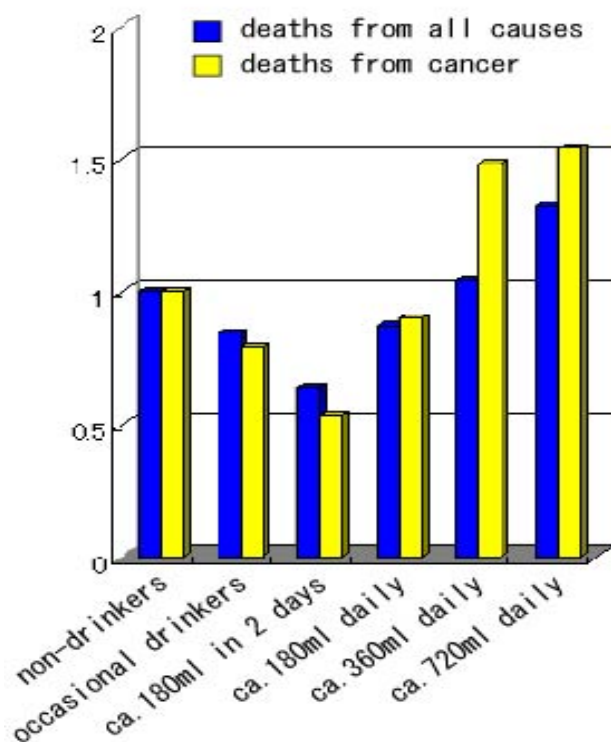


Fig.5: Relative risks of mortality from all causes and cancers

(3) Cancers in Those Who Drink Alcohol and Smoke

<http://epi.ncc.go.jp/jphc/outcome/04/inshto.html> (Japanese)

http://epi.ncc.go.jp/jphc/outcome/22/alcoh_can.html (Japanese)

The incidence of cancer in those who both drink alcohol and smoke cigarettes becomes significantly elevated as the amount of alcohol intake increases, in a completely different manner from that of those who only drink and do not smoke.

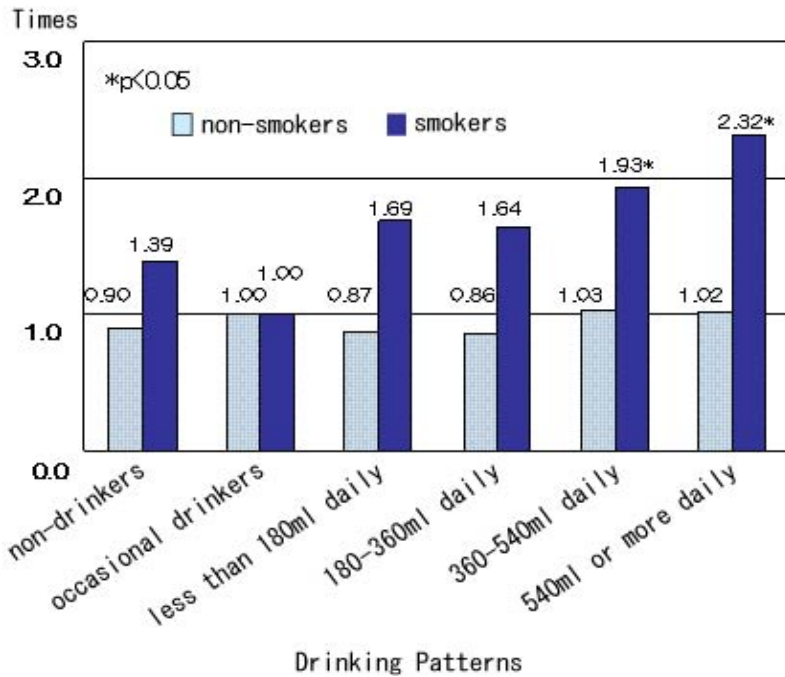


Fig.6: Cancer incidence by alcohol drinking for smokers and non-smokers (hazard ratios relative to occasional drinkers)

On the other hand, mortality rates from alcohol-related cancers (cancers of the oral cavity, larynx, pharynx, oesophagus and liver) were higher for those who drank roughly every second day, compared with occasional drinkers (1-3 days per month), and this trend was similar for both smokers and non-smokers.

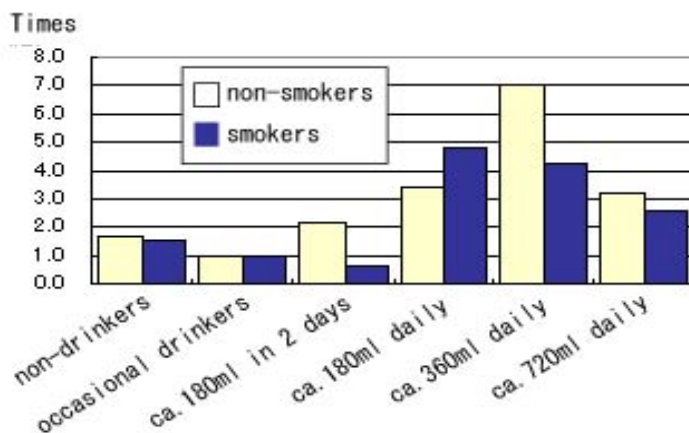


Fig.7: Relationships between mortality rates from alcohol-related cancers and drinking patterns - relative to the mortality rate of occasional drinkers

Rates of mortality from cancers other than "alcohol-related cancers" have different outcomes for smokers and non-smokers: while non-smokers exhibited no elevated cancer mortality with increasing amounts of alcohol consumed, smokers had a higher cancer mortality rate as alcohol intake increased. Though the reasons for these outcomes are uncertain, one hypothesis is that alcohol-metabolizing enzymes are also involved in activation of carcinogenic substances contained in the tobacco smoke. Thus, cancers other than "alcohol-related cancers" may exert effects on mortality risk substantially similar to those of "alcohol-related cancers" if smokers constitute a majority of the study population, which therefore requires a quite deliberately different study design.

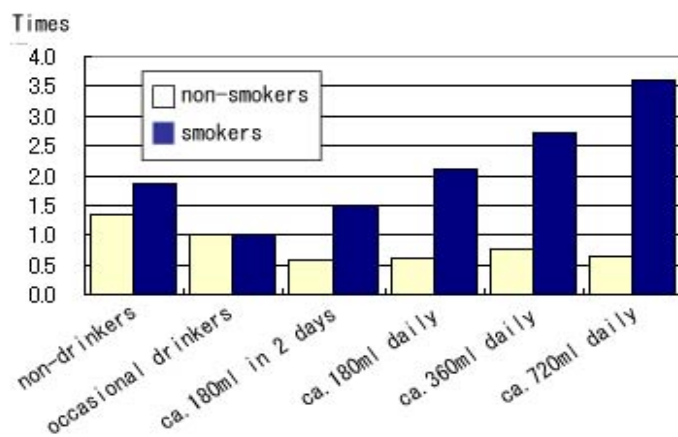


Fig.8: Relationship between drinking patterns and mortality rates from cancers other than alcohol-related cancers

(4) Magnitude of Effects of Combined Alcohol Drinking and Smoking

http://epi.ncc.go.jp/jphc/outcome/10/daich_1.html (Japanese)

Only sparse data are available for combined effects of alcohol drinking and smoking on cancer occurrence, except for one study on colorectal cancer.

The incidence of colorectal cancer among those whose average daily alcohol consumption was more than 360ml of Japanese sake (rice wine) or equivalent was 2.1 times greater than non-drinkers.

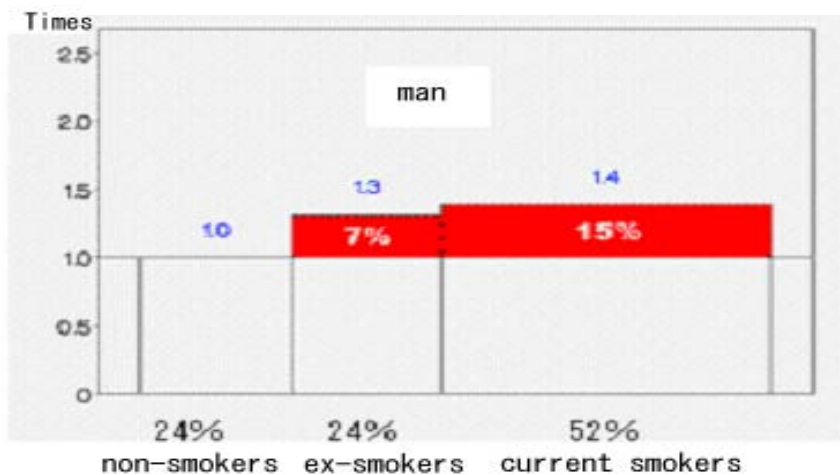


Fig. 9: Colorectal cancer incidence and alcohol consumption

On the other hand, the relative risk of colorectal cancer for current smokers was 1.4 compared with never-smokers (although IARC stated that "it is not possible to conclude that the association between tobacco smoking and colorectal cancer is causal" in the Summary of Data Reported and Evaluation of "tobacco smoking and tobacco smoke," which will be mentioned below).

In the above study, the colorectal cancer risk with average daily intake of 360ml or more of Japanese sake or equivalent in current smokers was estimated at 3, compared to non-smoking non-drinkers.

This estimated risk was much higher compared with the risk related to alcohol drinking alone or to smoking alone, suggesting synergistic effects of the combined risk factors. This may imply that cancer risk factors other than those for smoking-related cancers could also result in an enhanced probability of developing cancer, when combined with alcohol drinking. This observation may also be inferred from the figures shown in (3) Cancers in Those Who Drink Alcohol and Smoke.

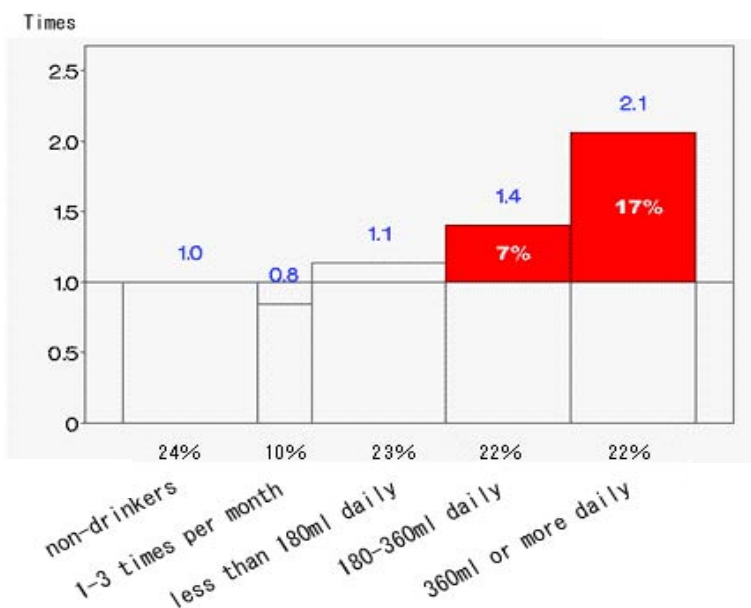


Fig. 10: Colorectal cancer incidence and cigarette smoking

5. Possibility of part of the elevated mortality associated with increased cumulative radiation doses being confounded by lifestyle-related factors to give false positive results

The analysis of lifestyle-related confounding factors, conducted in conjunction with the Phase II Epidemiological Survey on Low-Dose Exposure of Radiation Workers, concluded that "larger cumulative doses are associated with larger percentages of increased numbers of packs of cigarettes smoked, increased daily alcohol consumption, and the numbers of workers ever engaged in harmful operations; while they are inversely related to the percentages of those ever having undergone stomach cancer screening tests." Together with the results reported in the Japan Public Health Center-based Prospective Study, we may reasonably make the following remarks:

- (1) It is important to be aware that a multitude of confounding factors, such as those just mentioned do exist, and that cigarette smoking, in particular, which has a strong association with cancer, exerted a clear confounding effect. It is also worth noting that alcohol drinking, which has a synergistic effect with cigarette smoking, is associated with such confounding factors.
- (2) In recent IARC publications, a larger number of smoking-related cancers (i.e., cancers causally associated with smoking) have been reported, including cancers of major parts/organs of the human, suggesting significant association of smoking with cancer risk

Table1: WHO's IARC Summaries and Evaluation of "Tobacco Smoking and Tobacco Smoke"

Cancer site	Effect of cigarette smoking			Effect of quitting smoking
	Causal relationship with smoking	Effect of duration of smoking or number of cigarettes smoked	Comments (histological types of cancer, etc.)	
Oral cavity	⊙	+	Use of alcohol in combination with tobacco smoking greatly increases the risk of oral cancer.	○
Nasal cavity and paranasal sinuses	⊙	+	Increase in relative risk was clearly observed histologically (for squamous-cell carcinoma).	
Nasopharynx	○	+	The potential confounding effect by Epstein-Barr virus was not controlled for in the studies, but such an effect was not considered plausible for increased risk for nasopharyngeal cancer among smokers.	○
Oropharynx and hypopharynx	⊙	+		○
Oesophagus	⊙	+	Increase in relative risk is clearly observed histologically (for adenocarcinoma and squamous-cell carcinoma). Use of alcohol in combination with tobacco smoking greatly increases the risk (squamous-cell carcinoma).	
Stomach	⊙	+	Consistent association with tobacco smoking has been shown, apart from confounding by alcohol consumption and Helicobacter pylori infection.	○
Large intestine (colon/rectum)	*		Inadequate adjustment for various potential confounders could account for some of the small increase in risk that appears to be associated with smoking.	
Liver	⊙	+	Many studies have shown no attenuation of the association between smoking and liver cancer after adjustment/stratification for markers of hepatitis B/hepatitis C virus infection.	○
Pancreas	⊙	+	The risk of pancreatic cancer remains elevated after allowing for potential confounding factors such as alcohol consumption.	○
Larynx	⊙	+		○
Lung	⊙	+	Tabacco smoking increases the risk of all histological types of lung cancer (including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma and large-cell carcinoma).	○
Female breast	-		Most epidemiological studies have found no association with active smoking, after controlling for established risk factors.	

Cervix	⊙	+	The effect of smoking was not diminished by the adjustment for human papillomavirus.	
Endometrium	-		An inverse relationship of cigarette smoking with endometrial cancer is observed in most studies, after adjustment for major confounders. This pattern is stronger in post-menopausal women.	
Prostrate	*		The small excess observed in some analytical mortality studies can reasonably be explained by bias in the attribution of the underlying cause of death.	
Urinary tract	⊙	+	Tobacco smoking is a major cause of transitional-cell carcinomas of the bladder, ureter, and renal pelvis. Evidence from several studies indicated that renal-cell carcinoma is associated with tobacco smoking.	○
Leukaemia	⊙(myeloid leukaemia)	+	No clear evidence of any risk was seen for lymphoid leukaemia/lymphoma.	
Other	*		There is inconsistent and/or sparse evidence for association between cigarette smoking and other cancer sites.	

Causal relationship with smoking

⊙: Causally associated

○: Associated with risk increase

*: No causal relationship with cancer established

-: No association with increased cancer risk observed

Effect of duration of smoking or number of cigarettes smoked

+: Increased cancer risk is associated with longer duration of smoking or greater numbers of cigarettes smoked.

Effect of quitting smoking

○: A reduction in risk after quitting is observed.

-: Risk remains elevated even after quitting.

(blank): No descriptions

(3) A synergistic effect of smoking and drinking is observed. With respect to the occurrence of colorectal cancer, their combined effect is much larger than that of smoking or drinking alone.

(4) Risks for cancers other than "alcohol-related cancers" may be affected in a manner similar to alcohol-related cancers, when combined with smoking.

The above remarks suggest the possibility that part of the elevated cancer mortality associated with increased cumulative radiation doses are confounded by lifestyle-related factors to give false positive results. However, in order to prove or disprove this possibility, more quantitative data are needed for assessing the extent of cancer mortality/morbidity influenced by each of the major confounding factors, thus necessitating further studies.