

product intakes and stroke mortality [34]. Finally, any misclassification arising from the food-frequency questionnaire is likely to be unbiased and would have led to an under-estimation of the true association between diet and prostate cancer risk, rather than a systematic bias. Information on a wide range of non-dietary factors was also collected at the same time as the dietary questionnaire and was taken into account in the analysis. However, a major disadvantage was that each questionnaire only covered a limited number of foods, and portion size was not included, so that the total consumption of foods or nutrients could not be estimated and adjustment for total energy intake could not be made. Further, despite the long period of follow-up, the relatively low numbers of cases identified limited the power to detect small associations between dietary intake and prostate cancer risk. Some prostate cancers may have been missed among men migrating out of the study catchment areas. The person-years were adjusted accordingly using residence probabilities estimated from the Adult Health Study sub-cohort and although these residence probabilities were calculated according to birth cohort and time period for each city, it is possible that migration rates may differ by other factors, such as education level or social class. However, the overall migration rate was low, which suggests that any differential migration by social class would not have made an appreciable difference to the risk estimates. We were unable to analyse dietary associations by stage or grade of disease, although the low overall numbers would have made such a sub-analysis difficult to interpret. Finally, although the study participants are unique in the fact that they were exposed to the atomic bombings of Hiroshima and Nagasaki in 1945, most individuals had a low exposure to radiation and all analyses here are presented after adjustment for radiation dose.

In summary, data from this relatively large prospective study show that a high frequency of fish intake was associated with an increased risk of prostate cancer. No other food items, including soya products, were significantly associated with prostate cancer risk.

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Smoking and fracture risk: a meta-analysis

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Abstract Smoking is widely considered a risk factor for future fracture. The aim of this study was to quantify this risk on an international basis and to explore the relationship of this risk with age, sex and bone mineral density (BMD). We studied 59,232 men and women (74% female) from ten prospective cohorts comprising EVOS/EPOS, DOES, CaMos, Rochester, Sheffield, Rotterdam, Kuopio, Hiroshima and two cohorts from Gothenburg. Cohorts were followed for a total of 250,000 person-years. The effect of current or past smoking, on the risk of any fracture, any osteoporotic fracture and hip fracture alone was examined using a Poisson model for each sex from each cohort. Covariates examined were age, sex and BMD. The results of the different studies were merged using the weighted β -coefficients. Current smoking was associated with a significantly increased risk of any fracture compared to

non-smokers (RR=1.25; 95% Confidence Interval (CI)=1.15–1.36). Risk ratio (RR) was adjusted marginally downward when account was taken of BMD, but it remained significantly increased (RR=1.13). For an osteoporotic fracture, the risk was marginally higher (RR=1.29; 95% CI=1.13–1.28). The highest risk was observed for hip fracture (RR=1.84; 95% CI=1.52–2.22), but this was also somewhat lower after adjustment for BMD (RR=1.60; 95% CI=1.27–2.02). Risk ratios were significantly higher in men than in women for all fractures and for osteoporotic fractures, but not for hip fracture. Low BMD accounted for only 23% of the smoking-related risk of hip fracture. Adjustment for body mass index had a small downward effect on risk for all fracture outcomes. For osteoporotic fracture, the risk ratio increased with age, but decreased with age for hip fracture. A smoking history was associated with a sig-

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nificantly increased risk of fracture compared with individuals with no smoking history, but the risk ratios were lower than for current smoking. We conclude that a history of smoking results in fracture risk that is substantially greater than that explained by measurement of BMD. Its validation on an international basis permits the use of this risk factor in case finding strategies.

Keywords Body mass index · Hip fracture · Meta-analysis · Osteoporotic fracture · Smoking

Introduction

It is well established that smoking is associated with a reduction in bone mineral density (BMD) in postmenopausal women and men [1]. A meta-analysis has suggested that the risk of hip fracture may also be markedly increased [2]. In current smokers, the risk of hip fracture compared with non-smokers was similar in women up to the age of 50 years. However, it increased thereafter, to a risk ratio (RR) of 1.17 at 60 years, 1.41 at 70 years and 1.71 at 80 years. In 90-year-old women the risk ratio was 2.08 [2]. In population-based samples, the risk of other osteoporotic fractures also appears to increase [3], but this is not an invariant finding [4]. The risk of forearm fractures does not appear to increase among smokers [3, 5, 6].

Increased fracture risk may in part be due to the fact that patients who smoke have low BMD [1]. Studies adjusted for BMD suggest that the relative risk is only modestly adjusted downward [7]. In the meta-analysis of Law and Hackshaw [2], although the difference in bone density between smokers and non-smokers was not apparent at age 50, it became noticeable with increasing age, so that at age 80 bone mineral density at the hip was 0.45 SD lower in smokers, as compared with non-smokers. From the relationship between bone mineral density in the hip and hip-fracture risk, the risk ratio in smokers was estimated at 1.56, compared with a direct

estimate of 1.71 for hip fractures. This led the authors to suppose that the majority of any risk was attributable to decreased bone density.

The association between smoking and subsequent fracture risk has led to the inclusion of current smoking as a risk factor in assessment guidelines in the United States and Canada [8, 9], if not in Europe [11, 12, 13]. Since smoking is considered a risk factor, partly independent of BMD, intervention is recommended in smokers with a *T*-score for BMD of -1.5 , whereas in non-smokers the intervention threshold is set at -2.0 SD. Attention has focused recently on assessing fracture probability by using multiple risk factors, rather than BMD alone, to provide intervention thresholds [8, 14, 15]. This demands knowledge of the interrelationships between these risk factors. The aim of our study was to quantify, in an international setting, the risk associated with smoking for future fractures and to explore the dependence of this risk on age, sex, body mass index (BMI) and BMD.

Materials and methods

We studied 59,232 men and women, of whom 18% had a history of current smoking, taken from ten prospectively studied cohorts. Brief details of these cohorts appear below and are summarized in Table 1.

CaMos

The Canadian Multicentre Osteoporosis Study (CaMos) is a current, prospective age-stratified cohort. The study documents the incidence of fractures and risk factors in a random sample of 9,424 men and women aged 25 years or older, selected by telephone listings. The sampling frame is from nine study centers in seven provinces [16]. Individuals were characterized by interview. BMD was measured by DXA (Dual X-ray absorptiometry) at the hip, using the Hologic QDR in seven centers and the Lunar DPX Alpha in two centers.

Table 1 Details of cohorts studied

Cohort	Sample size	% Women	Person-years	Mean age (years)	Smoking history (%)		Any kind of fracture	Osteoporotic fracture	Hip fracture
					Current	Ever			
CaMos	9,401	69	26,656	62.1	-	54	586	316	42
DOES	2,163	61	16,333	70.7	8	41	532	418	107
EVOS/EPOS	13,841	52	41,429	63.8	20	52	731	731	50
Gothenburg I	2,320	61	16,255	78.7	15	41	424	424	332
Gothenburg II	7,012	100	29,335	58.9	25	49	433	438	29
Hiroshima	1,937	69	7,563	64.8	20	34	134	64	21
Kuopio	11,798	100	56,602	52.3	11	-	1,053	-	-
Rochester	998	65	6,212	56.8	-	47	289	244	42
Rotterdam	7,590	60	42,613	70.1	23	63	967	746	271
Sheffield	2,172	100	6,900	80.0	7	46	290	241	63
Totals	59,232	74	249,898	62.8	18	52	5,444	3,495	957

DOES

The Dubbo Osteoporosis Epidemiology Study (DOES) is a population-based study with multiple assessments of skeletal status in men and women from Dubbo, Australia, and at least 60 years old [17, 18]. Study participation was 56% of the population. Baseline measurements included BMD at the femoral neck, assessed using DXA (GE-Lunar, DPX and Prodigy). Fractures are identified through radiologists' reports from the two centers servicing the region.

EVOS/EPOS

The European Vertebral Osteoporosis Study (EVOS) comprised age- and sex-stratified random samples from 36 centers in 19 European countries [19]. Equal numbers of men and women were drawn in each center within six sequential 5-year age bands (from 50 to 79 years). A baseline radiograph for vertebral-fracture prevalence was undertaken in 15,570 men and women. BMD was measured in 3,461 men and women from 13 centers, by DXA at the femoral neck using pencil-beam machines cross-calibrated with the European spine phantom. The sample provided the framework for the European Prospective Osteoporosis study (EPOS), in which repeated assessment was undertaken in 29 of the centers [20, 21].

Gothenburg I

This study comprised four birth cohorts of 2,375 randomly sampled men and women aged at least 70, followed for up to 20 years in Gothenburg, [22, 23] after a baseline BMD measurement. Participants were drawn randomly from the Gothenburg population register by date of birth, to provide cohorts aged 70, 76, 79 and 85 years at the time of investigation. Bone mineral density was measured at the right heel using dual photon absorptiometry.

Gothenburg II

The Gothenburg study comprised a randomly drawn population cohort of approximately 7,000 women aged 21–89, followed for up to 7.9 years (mean = 4.2 years) [24]. Seventy percent of those invited participated in the study, which examined risk factors for osteoporosis through a standardized questionnaire. BMD was assessed at baseline at the distal forearm, using the Osteometer DTX 200.

Hiroshima

The Adult Health Study in Hiroshima (AHS) was established to document late health effects of radiation

exposure among atomic-bomb survivors in Hiroshima and Nagasaki. The original AHS cohort consisted of about 15,000 atomic-bomb survivors and 5,000 controls selected from residents in Hiroshima and Nagasaki, using the 1950 national census supplementary schedules and the Atomic Bomb Survivors Survey. AHS subjects have been followed through biennial medical examinations since 1958, with a participation rate of approximately 80%. BMD at the lumbar spine and proximal femur has been measured at each biennial health examination using DXA (Hologic QDR-2000) since December 1993. At each examination, trained nurses interviewed subjects about fractures and measured height and weight [25, 26].

Kuopio

The Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) study in Finland was based on a postal enquiry sent to all of the 14,220 women aged 47–56 residing in Kuopio province in 1989. Of these, 13,100 responded, 1,214 of whom were excluded due to incomplete information. This left a study population of 11,886 women. A random stratified sample of 3,222 underwent bone mineral densitometry at the femoral neck, with DXA using the Lunar DPX [27].

Rochester

The Rochester cohort was recruited from two random population samples stratified by decade of age. One sample included women who were followed for up to 20 years [28], and the other was composed of women and men followed for 8 years [29]. BMD of the right femoral neck was measured—by dual photon absorptiometry for the first cohort (cross-calibrated to DXA), and by DXA (Hologic QDR 2000) for the second group. Fractures were ascertained by periodic interview combined with review of the inpatient and outpatient medical records of all local care providers.

Rotterdam

The Rotterdam study, begun in 1990, was a prospective cohort study that aimed to examine and follow up on all residents aged 55 years and older living in Ommoord, a district of Rotterdam [30]. By 1993, 7,983 residents had been included (response rate 78%). Bone mineral density was assessed at the femoral neck by DXA, using a Lunar DPX-L. Fracture follow-up was done using an automated link with general practitioner computer systems and hospital admission data [31]. Fracture data were collected and validated by two independent research physicians. For this analysis, validated fracture follow-up was available for 7,590 participants (3,012 men), with an average follow-up time of 6 years.

Sheffield

The Sheffield cohort comprised women aged 75 years or older, selected randomly from the population of Sheffield, UK, and surrounding districts, between 1993 and 1999. Approximately 35,000 women, identified from general practitioner listings, were contacted by letter and invited for assessment of their skeletal status. Of the 5,873 women agreeing to attend the screening visit, 281 were excluded. The remainder were randomly allocated after they gave informed consent to treatment with the bisphosphonate clodronate, or to an identical placebo. This study is still in progress. The material used for the present paper included 2,148 women allocated to treatment with placebo [32]. All women had baseline assessment of BMD at the femoral neck, using the Hologic 4500. Outcomes were assessed by home visits at 6-month intervals.

Baseline and outcome variables

A history of current or past smoking was obtained by self-report. For the EVOS/EPOS, Hiroshima and Gothenburg I cohorts, this was recorded as past or current use of tobacco. For the Gothenburg II cohort, the same data were collected, but use for 6 months qualified as past or current use. For Rotterdam, Sheffield and DOES, tobacco use was recorded as previous, current or never. Data on current smoking was not available for two cohorts (CaMos and Rochester). Height and weight were measured using standard techniques in all cohorts. BMI was calculated as weight in kg divided by height squared in m. Bone mineral density was assessed by multiple techniques as described above. For the purposes of this analysis, we utilized BMD assessed at the femoral neck by DXA, with the exception of the Gothenburg cohorts, for which BMD was assessed by DPA at the heel and DXA at the distal forearm.

Fractures were ascertained from self-reports (Sheffield, Kuopio, EVOS/EPOS, Hiroshima) and/or verified from hospital or central databases (Gothenburg, CaMos, DOES, Sheffield, EVOS/EPOS, Rochester, Rotterdam). The EPOS study also included sequential systematic radiography to define incident vertebral deformities, but the data were not used in this analysis. Our analysis used information on any kind of clinical fracture and on clinical fractures considered to be osteoporotic. In addition, hip fracture was considered separately. An osteoporotic fracture was one that the investigator considered to be due to osteoporosis, except as indicated below. For the EVOS/EPOS study, osteoporotic fractures comprised hip, forearm, humeral or spine fractures. For the CaMos study, they comprised fractures of the spine, pelvis, ribs, distal forearm, forearm and hip. In the other cohorts (Sheffield, Rotterdam, Rochester, Gothenburg I and II, Hiroshima) fractures at sites considered characteristic for osteoporosis were

extracted [33]. Details about the number of participants, gender and fractures are provided in Table 1.

Statistical methods

The risk of fracture was estimated by Poisson regression, applied separately to each cohort and sex [32]. Covariates included time since start of follow-up, current age, history of smoking, and BMD. We also excluded BMD from the model. The beta coefficient for each sex in each cohort is age-dependent, $\beta_k + \beta_{k+1} \times \text{age}$. The estimated value of the β coefficients and their variance was determined for each age within the range of 50 to 85 years. Results of each cohort and both sexes were weighted according to the variance and merged to determine the weighted mean and standard deviations. The risk ratio of those who currently smoked or ever smoked versus those without a smoking history was equal to weighted e^{mean} . In further models, we examined the effects including BMI with and without BMD. There was little heterogeneity between cohorts in the relationship between hip-fracture risk and smoking ($I^2 = 12\%$; 95% CI (confidence interval) = 0–53%), and a fixed-effect model was used [34].

The component of the risk ratio explained by BMD was computed from a meta-analysis of BMD and fracture risk [35]. The risk of any fracture was assumed to increase 1.6-fold for each SD decrease in BMD. For hip fracture, the gradient of risk was assumed to be 2.6 per SD. The proportion of risk attributed to a low BMD was computed as

$$\frac{[\log \text{RR}_a / \log \text{GR}] - [\log \text{RR}_b / \log \text{GR}]}{[\log \text{RR}_a / \log \text{GR}]}$$

Where RR_a is the unadjusted risk ratio, RR_b is the risk ratio adjusted for BMD, and GR is the gradient of risk.

Results

Of 59,232 men and women studied, 867 men and 4,577 women were identified as having a subsequent fracture

Table 2 Prevalence of smoking history in men and women by age

Age (years)	Probability of smoking (%)		
	Men	Women	Combined
50	41.3	26.8	32.9
55	37.2	22.3	28.4
60	33.3	18.3	24.3
65	29.6	15.0	20.6
70	26.1	12.1	17.4
75	22.9	9.7	14.6
80	20.0	7.8	12.1
85	17.4	6.2	10.0

(any kind), of which 677 men and 2,817 women were characterized as osteoporotic. Of these, 207 men and 750 women sustained a hip fracture. The total follow-up in person years was 61,563 in men and 188,334 in women. BMD measurements were available in 36,550 individuals (64%) and BMI in 96%. The prevalence of smoking among the cohorts decreased almost linearly with age in men and women ($p < 0.001$; Table 2). At all ages, current smoking was higher in men than in women.

Current smoking

Current smoking was associated with a significantly increased risk of any kind of fracture, including osteoporotic or hip fractures taken alone, in both men and women (Table 3). For any kind of fracture and for osteoporotic fractures taken alone, the risk in smokers was significantly higher in men ($p = 0.015$) than in women ($p = 0.03$). For hip fractures taken alone, there was no difference in the risk ratio between men and women. For men and women combined, risk with current smoking was highest for hip fracture (RR = 1.84), lowest for fractures taken overall (RR = 1.25) and intermediate for osteoporotic fracture (RR = 1.29).

Risk ratio was adjusted downward somewhat when taking BMD into account (see Table 3). In women, for any fracture overall or osteoporotic fracture specifically, the associations between smoking and fracture were no longer significant. In men, the effect was less marked or not apparent. In men and women together, low BMD accounted for the minority of the risk associated with current smoking. For fractures overall, 45% of the risk was explained by BMD, whereas for osteoporotic fracture alone it was 40% and for hip fracture, only 23%.

Table 3 Risk ratio of fracture (RR) and 95% confidence interval (CI) associated with current smoking by fracture outcome in men and women

Outcome	Sex	RR	95% CI	RR*	95% CI
Any kind of fracture	M	1.50	1.26-1.77	1.49	1.20-1.84
	F	1.18	1.07-1.30	1.02	0.90-1.16
	M + F	1.25	1.15-1.36	1.13	1.01-1.25
Osteoporotic Fracture	M	1.53	1.27-1.83	1.54	1.21-1.95
	F	1.20	1.06-1.35	1.01	0.87-1.17
	M + F	1.29	1.17-1.43	1.13	1.00-1.28
Hip fracture	M	1.82	1.34-2.49	1.69	1.16-2.48
	F	1.85	1.46-2.34	1.55	1.16-2.07
	M + F	1.84	1.52-2.22	1.60	1.27-2.02

*Risk ratio adjusted for BMD

Table 4 Risk ratio (RR) for fracture in current smokers (men and women combined) adjusted for age, BMD, BMI and both BMD and BMI. CI confidence interval

Adjustment	Outcome fracture					
	Any		Osteoporotic		Hip	
	RR	95% CI	RR	95% CI	RR	95% CI
Age	1.25	1.15-1.36	1.29	1.17-1.43	1.84	1.52-2.22
Age BMD	1.13	1.01-1.25	1.13	1.00-1.28	1.60	1.27-2.02
Age BMI	1.19	1.09-1.30	1.21	1.08-1.34	1.65	1.34-2.03
Age, BMI, BMD	1.12	1.01-1.25	1.11	0.98-1.26	1.55	1.23-1.96

BMI

The risk ratios for smokers were also adjusted downward when account was taken for BMI, though all ratios remained significantly increased (Table 4). The downward adjustment was less than the adjustment for BMD alone. When smoking, BMI and BMD were entered into the model, a further decrease in risk ratio was observed, although the risk ratios remained above unity, significantly so for the risk of (any) fractures overall and for hip fracture.

Table 5 Risk ratio (RR) and 95% confidence intervals (CI) for osteoporotic and hip fractures in current smokers for men and women combined

Age (years)	Without BMD		Adjusted for BMD	
	RR	95% CI	RR	95% CI
(a) Osteoporotic fracture				
50	1.05	0.80-1.37	0.82	0.57-1.18
55	1.06	0.86-1.30	0.85	0.65-1.12
60	1.08	0.92-1.26	0.88	0.72-1.08
65	1.14	1.00-1.30	0.91	0.76-1.09
70	1.27	1.12-1.45	1.01	0.85-1.20
75	1.45	1.28-1.65	1.20	1.01-1.43
80	1.54	1.34-1.77	1.30	1.08-1.57
85	1.52	1.28-1.80	1.28	1.00-1.63
(b) Hip fracture				
50	2.52	1.24-5.10	2.28	0.94-5.51
55	2.35	1.32-4.19	2.09	1.03-4.24
60	2.17	1.38-3.44	1.87	1.07-3.25
65	1.98	1.38-2.86	1.68	1.07-2.65
70	1.92	1.42-2.60	1.69	1.15-2.48
75	1.94	1.52-2.49	1.76	1.30-2.37
80	1.91	1.55-2.35	1.69	1.31-2.19
85	1.80	1.43-2.26	1.57	1.16-2.13

Age

Risk ratios increased with age for any fracture and for osteoporotic fractures specifically, but they were significantly higher than unity at all ages (Table 5). With adjustment for BMD, current smoking was a significant risk only from the age of 70 years. In contrast, for hip fracture risk, the risk ratio decreased with age but was significantly higher than unity at all ages with or without adjustment for BMD.

Ever-smokers

A history of smoking (ever smoked) was also associated with a significant risk increase for any fracture, and, specifically, for an osteoporotic or hip fracture (Table 6). The risk ratios were lower than for current smoking (see Table 3), but, just as in that case, were highest for hip fracture. There was no significant difference in risk ratio between men and women, no difference when adjusted for BMD, and no significant effect of age on the risk ratio (data not shown). The exclusion of data from the Gothenburg cohorts (where BMD was assessed at the heel or forearm) had no material effect on these results (data not shown).

Discussion

The present study confirms that a history of smoking carries a modest but significant risk for future fractures. In addition, the effect of smoking is over and above that which can be explained by variations in BMD. The risk of subsequent fractures was greater in the case of hip fracture than for all fractures, and intermediate for osteoporotic fractures. For hip-fracture risk in women, the increase in risk ratio (1.85) was comparable to that described in the meta-analysis from Law and Hackshaw [2]. In their findings, risk ratios increased with age; however, in the present study risk ratios for hip fracture tended to decrease with age. In contrast, risk ratios for osteoporotic fractures (which included hip fractures)

increased with age. The strength of the association we found was lower than for ever-smokers, consistent with the view that the effect of smoking appears to wane slowly after a person stops smoking [36].

A particular strength of the present study is that the estimate of risk is from an international setting, from randomly or quasi-randomly selected population cohorts, and the calculations were based on the primary data. This decreases the risk of publication and selection biases, which may have large effects. For example, in the large, prospective study from Kuopio, the risk of fracture for current smokers was 1.47 (95% CI = 1.05–2.06) when the sample included individuals selected on the basis of risk factors. From the random population sample used in the present study, the relative risk for fractures overall was 1.18 (95% CI = 0.70–2.00) [3]. Furthermore, the consistency of the association within cohorts indicates the generalizability of this risk factor's importance.

The large sample size studied permitted us to examine risk by age. For all fractures and for osteoporotic fractures specifically, the risk ratios were relatively constant with age. If anything, they tended to increase with age. In the case of hip fracture, risk ratios decreased with age, but this was not significant. Much larger samples would be needed to verify such an effect. A limitation of this study was that we were unable to examine the dose dependency of the association, due to differences in the way that smoking histories were obtained. In this regard, men tend to smoke more than women. This may account for the slightly higher risk ratios observed in men.

The present study also quantifies the independent contributions of low BMD or BMI to the risks associated with smoking. Low BMD explained a minority of the total risk, contradicting the findings of Law and Hackshaw [2] but agreeing with others [7]. With regard to BMD, there are several mechanisms whereby smoking might adversely affect fracture risk. Female smokers may have increased rates of bone loss after menopause [37], but this is not consistently found [38, 39]. Smoking women also have earlier menopause [37, 40, 41]. It has been suggested that smoking may enhance estrogen catabolism [42]. The effects of hormone replacement therapy (HRT) have in some, but not all, studies been attenuated among smokers [43, 44]. Smokers are also thinner and, hence, have lower body mass index [40, 45]. Consequently, the protective effect of adipose tissue and peripheral estrogen metabolism is impaired. Bone loss is reported to be higher in male smokers than in female smokers [38], perhaps due to men's higher exposure to cigarette smoking. We observed higher risk ratios for men than for women for any fracture and for osteoporotic fracture specifically. Such effects may explain the component of fracture risk that is attributable to low BMD or BMI. However, as shown in the present study, this represents a minority of the risk.

The mechanism for the BMD-independent increase in risk could not be determined from this study. Possibly, it results, in part, from lower levels of physical activity or

Table 6 Risk ratio (RR) associated with a smoking history by subsequent fracture outcome in men and in women. RR is not adjusted for BMD

Outcome	Sex	RR	95% confidence interval
Any fracture	M	1.27	1.07–1.51
	F	1.18	1.10–1.26
	M + F	1.19	1.12–1.27
Osteoporotic fracture	M	1.34	1.10–1.63
	F	1.15	1.07–1.25
	M + F	1.18	1.09–1.27
Hip fracture	M	1.11	0.67–1.83
	F	1.42	1.18–1.72
	M + F	1.38	1.15–1.65

to co-existing morbidity, which might in turn increase the risk of falls or impair protective responses to injury [46, 47, 48]. It is also possible that smoking-induced changes in the microarchitecture of cancellous bone would weaken the resistance to mechanical force out of proportion to any effect on BMD. Finally, errors in measurement of BMD [49] will result in the underestimation of bone's contribution to fracture risk.

Whatever the mechanism involved, these data indicate that the risk of fractures is greater for smokers and those with a history of smoking than it is for individuals of the same age, sex and BMD who do not or did not smoke. This has implications for intervention thresholds. Health economic analyses suggest that intervention is cost-effective when treatment is targeted to women with a *T*-score of -2.5 SD at the femoral neck [15]. Since smoking carries a risk over and above that provided by BMD alone, intervention thresholds for BMD can be less stringent in smokers and still yield the same cost-effectiveness. This approach has been incorporated into health economic analyses [8, 50]. However, a large number of additional and stronger independent risk factors for fracture have been identified. These include a history of fracture, corticosteroid exposure, a family history of fracture, secondary osteoporosis, and possibly the biochemical indices of bone turnover [15, 51, 52, 53, 54]. Before these risk factors can be readily used for assessing fracture risk in the general population, their interrelationships will need to be determined.

We conclude that a history of smoking results in a substantial risk for future fractures and that this risk is largely independent of BMD. The fact that this association holds up on an international scale provides a rationale for using this risk factor in case-finding strategies. Moreover, identified patients can be targeted for treatment at lower BMD thresholds than are non-smoking individuals of the same age who have osteoporosis.

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Uncertainty in estimating probability of causation in a cross-sectional study: joint effects of radiation and hepatitis-C virus on chronic liver disease

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Abstract

Exposure to other risk factors is an important consideration in assessing the role played by radiation in producing disease. A cross-sectional study of atomic-bomb survivors suggested an interaction between whole-body radiation exposure and chronic hepatitis-C viral (HCV) infection in the etiology of chronic liver disease (chronic hepatitis and cirrhosis), but did not allow determination of the joint-effect mechanism. Different estimates of probability of causation (POC) conditional on HCV status resulted from additive and multiplicative models. We therefore estimated the risk for radiation conditional on HCV status using a more general, mixture model that does not require choosing between additivity or multiplicativity, or deciding whether there is interaction, in the face of the large uncertainty. The results support the conclusion that POC increases with radiation dose in persons without HCV infection, but are inconclusive regarding individuals with HCV infection, the lower confidence bound on estimated POC for radiation with HCV infection being zero over the entire dose range. Although the mixture model may not reflect the true joint-effect mechanism, it avoids restrictive model assumptions that cannot be validated using the available data yet have a profound influence on estimated POC. These considerations apply more generally, given that the additive and multiplicative models are often used in POC related work. We

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therefore consider that an empirical approach may be preferable to assuming a specific mechanistic model for estimating POC in epidemiological studies where the joint-effect mechanism is in doubt.

1. Introduction

Probability of causation (POC) for radiation exposure is a topic of considerable current interest with many remaining unsolved problems. Problems with the definition of POC and difficulties in its estimation via the attributable fraction have been discussed [1–4], with the term ‘assigned share’ (AS) often used in place of POC. In reality, a radiation exposed person’s disease either was or was not related to his or her radiation exposure but, in the absence of a clear radiation fingerprint, it cannot be determined definitively whether radiation played a role. Instead, the likelihood of radiation involvement (the POC) is estimated from epidemiological studies as the proportion of similar persons whose disease was statistically related to radiation exposure—the so-called attributable fraction. One problem is that study populations that are sufficiently large to detect associations typically include substantial heterogeneity, and it is not usually possible to simultaneously adjust for all factors related to this heterogeneity. Another problem is apportioning the risk when there is interaction between radiation and other risk factors.

Most studies of interaction and POC have been in terms of incidence and relative risk models for the joint effects of smoking and radon exposure on lung cancer etiology, which appears to be between additive and multiplicative (see [5–9]). Although many treatments of the problem of estimating POC rely on the additive and multiplicative models or their mixture for assessing joint effects, other models have been used to derive estimates of POC or related measures (see [10–12]). As demonstrated by Land *et al* [13], who successfully compared additive versus multiplicative models for breast cancer, epidemiological studies may be able to discriminate between certain extreme forms of interaction. However, epidemiological studies typically lack the statistical power to make inference about more subtle mechanistic effects, such as an independent, multiplicative joint effect versus super-multiplicative synergism or, in the case of radon and smoking joint effect on lung cancer in the aforementioned references, multiplicative versus sub-multiplicative. Beyea and Greenland [14] recommended that calculated values of POC be accompanied by precise statements of the underlying biological model assumed and the definition of causation employed. Although we agree that this is important, the issue of what is the correct biological model may often be difficult to resolve using epidemiological data, where unmeasured confounding or effect-modifying factors can render the observed interaction different from that predicted by the underlying, true mechanism. This leaves open the possibility of wrongly selecting an overly simple model (e.g., not including an interaction term in the multiplicative or additive model) simply because there is inadequate power to detect the interaction. Therefore, a POC may be reported for a well described model that is wrong.

Previous studies have not adequately addressed the problem of joint risk factors and POC in the context of non-cancer disease prevalence measured in a cross-sectional study. Furthermore, published work to date does not elucidate the effect on POC of the choice of mathematical function relating the occurrence of disease to the measure of risk (e.g., relative risk versus odds ratio). The goal of our research was to examine POC for non-cancer disease prevalence using the odds ratio rather than the relative risk. We investigated the joint effect of radiation and hepatitis-C virus (HCV) on the prevalence of chronic liver disease (chronic hepatitis and liver cirrhosis) in atomic-bomb survivors. Uncertainty about the underlying model for the

joint effect translated into uncertainty about POC to such a large degree that estimates of POC based on any specific mechanistic model for the joint effect were virtually useless. As an alternative, we fitted a more general mixture model for the joint effect and avoided the problem of apportioning joint risk by calculating POC for radiation conditional on the HCV infection status. We concluded that, although the mixture model may not be the most appropriate model from a mechanistic standpoint, epidemiological data often do not allow us to make a precise inference about the form of the joint effect and may include undetected (lurking) effects due to unmeasured factors. Thus, when estimating POC from epidemiological data it may be preferable to base it on the observed data using a general model rather than to report POC based on a specific joint-effect model for which systematic errors cannot be adequately evaluated due to unadjusted effects or a lack of statistical power.

2. Probability of causation and conditional attributable fraction

In a cross-sectional study, such as the study of liver disease in atomic-bomb survivors [15] (described in section 3), the classical POC can be estimated by the attributable fraction (AF), the proportion of disease prevalence that is related to radiation exposure in an epidemiological study population. For a chronic disease such as cirrhosis or hepatitis, the prevalence may be estimated by a model

$$P(D|x),$$

where P is the probability of disease D occurrence as of the study time, given radiation dose x . The attributable fraction at dose x is

$$AF(x) = \frac{P(D|x) - P(D|0)}{P(D|x)}, \quad (1)$$

where $P(D|0)$ is the prevalence of disease not related to exposure, the background prevalence. $AF(x)$ is then used as an estimate of the probability that exposure to dose x resulted in disease in an individual. It is a valid estimate of probability if the function $P(D|x)$ is non-decreasing in x . The most common estimate of POC, the assigned share (AS), is derived from equation (1) by assuming a relative risk model for the instantaneous probability (i.e., incidence) of disease occurrence:

$$AS(x) = \frac{P(D|0)[RR(x) - 1]}{P(D|0)RR(x)} = \frac{ERR(x)}{1 + ERR(x)} \quad (2)$$

where $ERR(x) = [P(D|x) - P(D|0)]/P(D|0)$ is the excess relative risk function, the relative risk [$RR(x) = P(D|x)/P(D|0)$] minus unity [5].

Traditional POC estimates have not taken other factors into account, and therefore have suffered from several problems, including heterogeneity in background disease occurrence. An epidemiological study cannot estimate the proportion of cases related to radiation in separate, homogeneous groups based on other, non-radiation factors if the stratification is so fine that each stratum contains few individuals. However, coarser stratification means that inadequately adjusted effects of other factors can render the radiation POC estimate less relevant to the specific spectrum of multiple risk factors to which any particular individual is exposed. It is therefore desirable to base calculation of POC on as many risk factors as possible given the limitations of epidemiological research. Our example considers one additional risk factor, but more non-radiation risk factors can be handled in a similar fashion as long as an appropriate risk regression model is fitted to the epidemiological data.

A model that estimates prevalence of liver disease as a function of joint hepatitis viral status v ($v = 1$ if infected, 0 if not) and radiation dose x predicts the prevalence for joint viral- and radiation-exposure status,

$$P(D|x, v)$$

and produces a conditional attributable fraction for radiation,

$$AF(x|v) = \frac{P(D|x, v) - P(D|0, v)}{P(D|x, v)}. \quad (3)$$

Note that conditioning means v is fixed in all terms of equation (3). This demonstrates that conditioning on viral infection status is equivalent to including viral status in the background prevalence. Thus, all excess prevalence of disease, which would not have occurred in the absence of radiation exposure, is attributed to radiation even though it might not have occurred with radiation exposure in the absence of concurrent infection with HCV virus (i.e., if there is mechanistic interaction between x and v). We return to this point in the discussion.

Using equation (1) to calculate POC can give a false impression of the effect of dose x on an individual, because it is based on the full population, which includes both HCV⁺ persons and HCV⁻ persons. An individual might have a very different radiation attributable fraction of liver disease depending on whether or not he or she is infected with HCV, but use of equation (1) is tantamount to assuming that x and v have independent mechanistic effects, and therefore equivalent to assuming that the radiation attributable fraction is the same regardless of HCV status. The extent to which HCV viral infection impacts the POC for radiation exposure is illustrated in the following section.

3. Additive and multiplicative risk models for chronic liver disease prevalence

Whole-body irradiation has been associated with chronic liver disease and liver cancer in the atomic-bomb survivors [16, 17], but because such irradiation is also associated with hepatitis-B virus (HBV) infection [18], a known risk factor for chronic liver disease including cancer, all or part of the perceived radiation effect on liver disease could be due to confounding by HBV. Although radiation is not associated with HCV prevalence [15], HCV-infected individuals have a higher risk of liver cancer for radiation exposure than uninfected individuals [19]. Given the rapid increase in rates of liver cancer in Japan [20, 21], which parallels a concurrent rise in HCV prevalence in recent decades, it is important for radiation protection and POC purposes to better understand the joint effect of radiation and HCV on the etiology of chronic liver disease. This is especially important because radiation risk estimates derived from the atomic-bomb survivor population are extrapolated to populations with low prevalences of HBV and HCV. Discrimination is needed between the following possible joint effects of C viral hepatitis and radiation on liver disease: (1) no biological interaction, (2) effect modification with radiation POC independent of HCV, or (3) effect modification including synergism. Following Greenland and Rothman [22], we assume an additive joint risk model in the case of no biological interaction, a multiplicative joint risk model without statistical interaction in the case of independent effects demonstrating effect modification, and a multiplicative model with positive statistical interaction (super-multiplicative) in the case of effect modification including synergism.

Anti-HCV antibody was measured in 6121 participants of the Adult Health Study of atomic-bomb survivors during medical examinations conducted between 1992 and 1994, as described elsewhere [15]. The data are summarised in table 1. In analysing the relationship between A-bomb radiation and chronic liver disease, we excluded 108 persons chronically

Table 1. Summary of the liver disease data and associated factors (numbers of diseased and total subjects).

Factor	Level	Radiation dose (shielded kerma, Gy)									
		0		>0, ≤1		>1, ≤4		>4		All	
		Diseased ^a	Total	Diseased	Total	Diseased	Total	Diseased	Total	Diseased	Total
City	Hiroshima	117	1379	101	1533	44	447	5	34	267	3393
	Nagasaki	33	869	22	528	18	365	2	22	75	1784
Gender	Male	65	800	56	636	31	309	4	25	156	1770
	Female	85	1448	67	1425	31	503	3	31	186	3407
Anti-HCV titer	<5	72	2027	64	1893	34	739	4	51	174	4710
	≥5	78	221	59	168	28	73	3	5	168	467
Age at examination	<50	9	234	10	174	1	18	1	2	21	428
	50–59	20	339	13	301	13	157	2	15	48	812
	60–69	74	930	64	804	31	385	3	27	172	2146
	70+	47	745	36	782	17	252	1	12	101	1791
Total		150	2248	123	2061	62	812	7	56	342	5177

^a Chronic hepatitis (ICD-9 571.4), liver cirrhosis (ICD-9 571.5), or unspecified liver disease (ICD-9 571.9), excluding cancer of the liver.

infected with HBV (positive for hepatitis-B surface antigen), including four persons who were jointly infected with HBV and HCV (joint infection is rare [23]). In addition, 833 subjects with unknown radiation doses and three who were diagnosed with liver cancer (ICD-9 155.0 or 155.2) were excluded, leaving a study group of 5177 persons. Shielded kerma was used rather than absorbed liver dose because viral infection is related to immune function, for which whole-body exposure is relevant, and liver dose is highly correlated with shielded kerma. A diagnosis of chronic liver disease other than cancer was made in 342 participants, of whom 168 (49%) were positive for anti-HCV antibody (titer ≥ 5). Diagnoses included chronic hepatitis (ICD-9 571.4; 300 subjects, 145 HCV⁺), liver cirrhosis (ICD-9 571.5; 31 subjects, 20 HCV⁺), or unspecified liver disease (ICD-9 571.9; 11 subjects, 3 HCV⁺). Chronic C viral hepatitis was diagnosed if the individual was positive for anti-HCV antibody and levels of either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were elevated continuously for more than six months. In Japan, approximately 50% of liver cirrhosis and chronic hepatitis are related to HCV (about 20% to HBV and about 12% to alcohol). This study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation.

Fitting models to absolute prevalence can be problematic when the prevalence is high (it is bounded by a maximum value of 1.0), as it is for HCV⁺ persons who were exposed to high doses of radiation. We therefore fit the odds of disease: $f(P) = P/(1 - P)$ (appendix). The joint effect of HCV infection and radiation on the odds of liver disease can be described using models based on the excess relative odds for HCV infection ($ERO(v) = \gamma$ when $v = 1$) and the excess relative odds for radiation ($ERO(x) = x\beta$, where β is the excess in the odds ratio per unit dose x , in Gray). An additive model for the joint effect is

$$f[P(D|x, v)] = f[P(D|0, 0)] \times (1 + x\beta + v\gamma) \quad (4)$$

and a multiplicative model is

$$f[P(D|x, v)] = f[P(D|0, 0)] \times (1 + x\beta) \times (1 + v\gamma), \quad (5)$$

where the background prevalence $P(D|0, 0)$ depends on city, gender, and age through the relationship $f[P(D|0, 0)] = \exp\{\alpha_0 + c\alpha_{\text{city}} + s\alpha_{\text{gender}} + a\alpha_{\text{age}} + a^2\alpha_{\text{age-squared}}\}$ with c and s

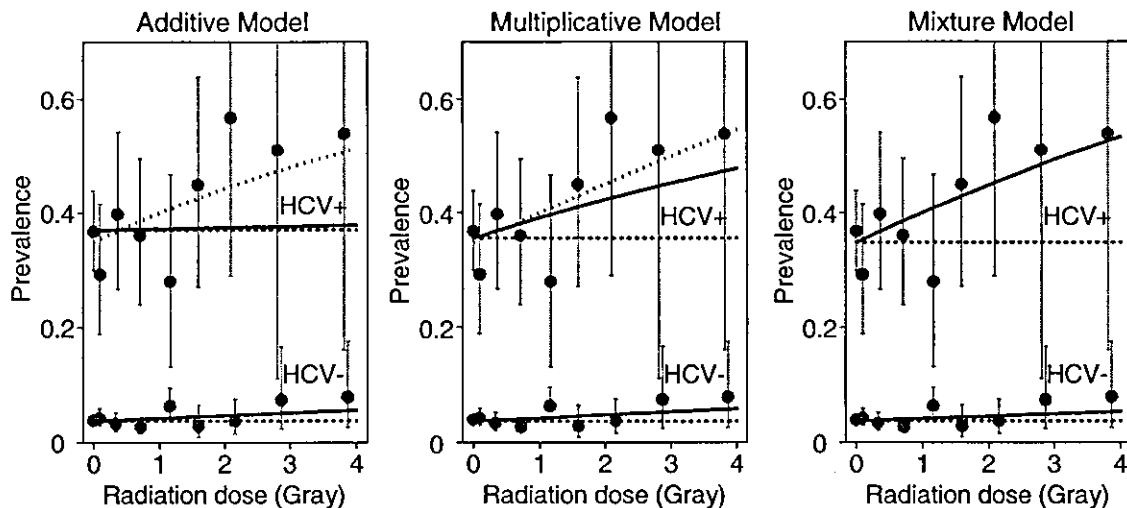


Figure 1. Prevalence of liver disease. Points are city-, gender-, and age-adjusted prevalences grouped by dose with 95% confidence intervals. Solid lines were derived from the models described in table 2 fit to individual (ungrouped) data. The horizontal dotted lines represent the background (no radiation exposure) prevalence depending on viral hepatitis infection status. The fitted models with interaction parameters (table 2) are shown as thin dotted lines for HCV⁺ subjects.

being city and gender indicator variables (0 for Hiroshima, 1 for Nagasaki; 0 for males, 1 for females) centred at their means (0.387 for city, 0.655 for gender) and a is age at examination centred at 62.5. Departure from either of these two specific models can be tested by adding an interaction term (the cross-product of x and v ; appendix). The estimated parameters and interaction terms from the fits of these models are shown in table 2, where it can be seen that there is a 25-fold increase in the slope of the odds of liver disease for radiation with concurrent HCV infection according to the additive model (interaction $p = 0.087$) but only a ninefold increase according to the multiplicative model (interaction $p = 0.54$). The fits are displayed in figure 1, which shows that the additive and multiplicative models without interaction terms produced quite different fits to the data, even though the interaction term for the additive model was only marginally significant.

In summary, it is not possible to clearly discriminate between the additive and multiplicative models, and there is no appreciable evidence for super-multiplicative synergism. Owing to a small number of heavily exposed HCV⁺ individuals (reflected in the wide confidence intervals on the grouped points in figure 1), there was little difference in the goodness of fit (deviance [24]) of these models (table 2), so it is not possible to conclude with certainty that one fits better than the other. Models fitted without the odds link (i.e., using the identity link $f(P) = P$) did not fit as well as with the odds link; the deviance was higher by about 4.0–4.5 for all models (results not shown). Examination of the fits in figure 1 shows that the fitted dose responses were very nearly linear with the odds link.

Estimates of conditional POC (equation (3) and appendix) derived from the additive and multiplicative models of table 2 (without interactions) are shown in figure 2. The curves conditional on HCV status under the multiplicative model of independence were not the same, as they would be using the traditional POC formula derived for disease rates [5]. This is because the odds of disease were modelled, and points out an important fact: the joint effect of two factors depends on the mathematical function (the so-called 'link function' [24]) relating the disease occurrence to the effects (e.g., ERR versus ERO) as well as the scale of the joint effect (e.g., additive versus multiplicative). Therefore, there is the potential for incorrectly

Table 2. Fits of various models for the radiation–HCV joint effect on the odds of chronic liver disease.

Parameter	Estimate (95% bounds)					
	Additive model		Multiplicative model		Mixture model ($\theta = 2.0$) ^a	
Background prevalence ^b ($100 \times \exp\{\alpha_0\}$, %)	3.8	(3.1, 4.7)	3.8	(3.0, 4.6)	3.8	(3.1, 4.6)
City (α_{city})	-0.69	(-0.98, -0.41)	-0.70	(-0.99, -0.42)	-0.70	(-1.00, -0.42)
Gender (α_{gender})	-0.54	(-0.79, -0.30)	-0.54	(-0.79, -0.30)	-0.55	(-0.79, -0.30)
Age (α_{age})	-0.004	(-0.019, 0.011)	-0.004	(-0.019, 0.011)	-0.004	(-0.019, 0.011)
Age-squared ($\alpha_{age-squared}$)	-0.0012	(-0.0022, -0.0003)	-0.0012	(-0.0022, -0.0002)	-0.0012	(-0.0022, -0.0002)
HCV (ERR_Y)	14.4	(10.8, 19.2)	13.7	(10.4, 17.9)	13.0	(9.9, 17.1)
Radiation (ERR_X , per Gy)	0.14	(-0.07, 0.44)	0.17	(-0.01, 0.41)	0.12	(-0.01, 0.29)
Deviance:	2044.15		2042.52		2042.21	
With interaction term						
HCV	13.1	(9.4, 18.1)	13.0	(9.4, 17.8)		
Radiation ($v = 0$)	0.13	(-0.07, 0.43)	0.12	(-0.07, 0.41)		
Interaction ($v = 1$) ^c	3.24	(-1.20, 9.70)	1.11	(0.80, 1.55)		N/A
		1-sided $p = 0.087^d$		2-sided $p = 0.54^e$		
Deviance	2042.30		2042.14			

^a θ is the mixture parameter of the mixture model as defined in text equation (6).

^b Due to covariate centring, the background represents the average over city and sex for 62½ year old individuals.

^c The HCV–radiation interaction with the additive model is the difference in $ERO(x)$ (incremental difference in excess relative odds), in the presence of HCV infection (appendix, equation (A.3)). The interaction with the multiplicative model is the logarithm of the relative difference in the odds ratios for a difference of 1 Gy in dose, in the presence of HCV infection (appendix, equation (A.4)).

^d The 90% likelihood-based lower confidence bound for the additive interaction term is 0.16. A one-sided test was used because sub-additivity is unlikely. The slope of the radiation dose response for $v = 1$ (HCV+) is the sum: radiation ($v = 0$) plus interaction ($v = 1$).

^e A two-sided test was used because there was no reason to assume *a priori* that interaction was either super-multiplicative (greater than multiplicative) or sub-multiplicative (between additive and multiplicative).

calculating POC with the traditional AS formula when the fit is based on disease odds rather than disease prevalence or rate (compare the formulae for AF to those for AF^O in the appendix).

Because of the much higher excess relative odds for HCV compared to that for radiation, the POC for radiation was insignificant in the presence of HCV infection with the additive model, but was substantial regardless of HCV status with the multiplicative model. We estimated the POC without regard for HCV status according to equation (1) (also shown in figure 2). Because of the low HCV prevalence, ignoring HCV if the true joint effect is additive results in a POC estimate close to that for HCV⁻ individuals. As is apparent from the lower portion of table 2, adding interaction terms to the additive and multiplicative models results in similar fits and—as may be intuitive—similar estimates of POC. However, in the absence of strong evidence for interaction with both models, the investigator might decide to use either the simple additive model or the simple multiplicative model based on subjective grounds, resulting in very different values of POC. Some might prefer the multiplicative model because of its slightly (though not statistically significant) lower deviance value, but this alone is not a suitable means of model selection because other, non-statistical, considerations may

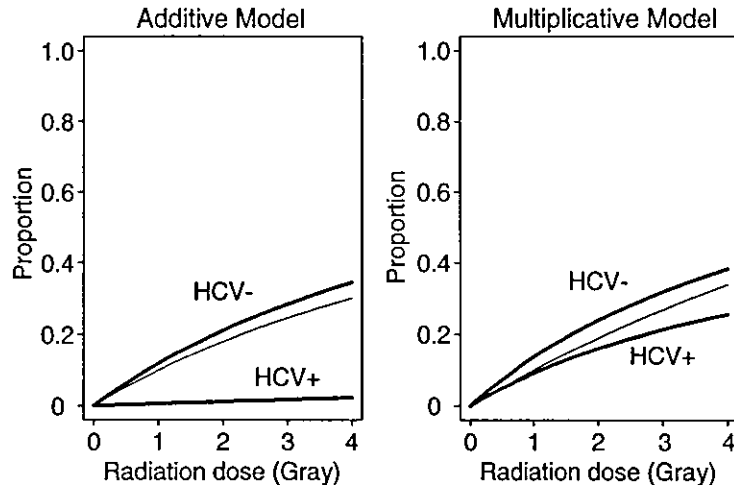


Figure 2. Probability of causation (POC) of liver disease for radiation estimated according to the additive or multiplicative model without statistical interaction. Estimates are conditional on HCV infection status. The baseline prevalence with no HCV infection and no radiation exposure ($P(D|0, 0)$; equations (4) and (5)) factors out of the POC calculation, so these curves do not depend on city, gender, or age at examination. The estimated POC for radiation derived without regard for HCV status (equation (1)) is shown for comparison (thin curve).

also apply. To avoid disputation over the choice between additive and multiplicative models that might arise in such a situation, we prefer using a more general empirical model that does not allow for such ambiguity in choosing between models.

4. A general, empirical mixture model

There are many forms of mixture model that include the additive and multiplicative models as special cases [25]. For reasons of computational convenience fitting the models in the Epicure software (Hirosoft International Corp., Seattle, WA), we used the following form:

$$f[P(D|x, v)] = f[P(D|0, 0)][(1 + x\beta) \times (1 + v\gamma)]^\theta [1 + x\beta + v\gamma]^{1-\theta}. \quad (6)$$

The multiplicative model is given by $\theta = 1$ and the additive model by $\theta = 0$. Other values of the mixture parameter θ reflect departures from pure additivity or pure multiplicativity. For example, $0 < \theta < 1$ represents super-additivity but sub-multiplicativity, and $\theta > 1$ is analogous to super-multiplicativity. We estimated θ using profile likelihood, maximizing the likelihood with respect to all other parameters for fixed values of θ and selecting the value of θ that resulted in the smallest deviance: $\theta = 2.0$ (figure 3). The resulting conditional POC is shown in figure 4 based on anti-HCV antibody status.

An approximate confidence interval for the mixture parameter is given by the values of θ for which the profile deviance increases by an amount specified by the chi-square distribution [24]. Due to flatness at $\theta > 2.0$, an upper bound on θ could not be estimated. An approximate 95% one-sided lower confidence limit for θ is given by the value θ_L for which the difference in deviance from the best-fitting model is 2.706 (the 90% cumulative level of the chi-square distribution with one degree of freedom): $\theta_L = -0.37$. Thus, the resulting confidence interval includes $\theta = 0$, representing the pure additive model, which is consistent with our finding that a one-sided test of non-additivity was not significant at the 5% level ($p = 0.087$). The resulting lower bounds on POC by anti-HCV antibody status are displayed in figure 4. These bounds demonstrate strong evidence in support of a dose-dependent increase in POC for radiation in

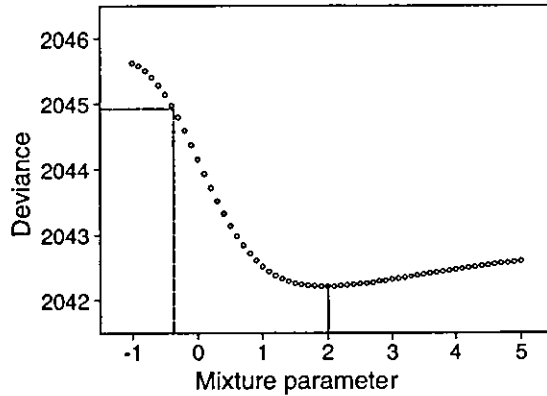


Figure 3. Estimation of the mixture-model mixture parameter by maximum profile likelihood. The best-fitting model was that with $\theta = 2.0$ (solid vertical line; minimum deviance = 2042.21). The one-sided 95% lower bound, -0.37 , was derived as the point where the deviance increased by 2.706 (i.e., deviance was 2044.92; dashed lines), the 90% level of the chi-square distribution with one degree of freedom.

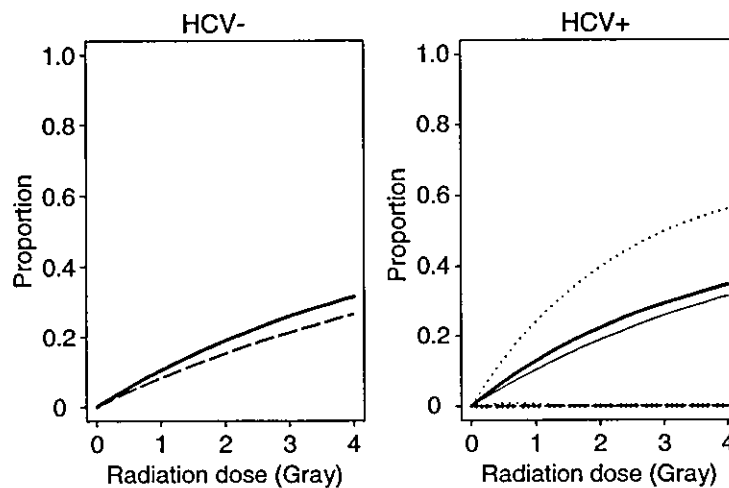


Figure 4. Probability of causation for radiation with the mixture model, conditional on viral infection status (solid curves). The dashed lines are the lower bounds on POC based on the profile likelihood for the mixture parameter. The dotted lines in the HCV⁺ panel represent bounds on the POC derived from 95% confidence bounds on the multiplicative interaction parameter (see text), which does not apply to the HCV⁻ situation. The estimated POC for HCV⁻ is shown in the HCV⁺ panel (thin curve) for comparison.

the absence of HCV infection, but the radiation POC is highly uncertain in the presence of HCV infection.

We also computed approximate bounds on POC for the HCV⁺ situation by using the likelihood bounds on the exponentiated multiplicative interaction parameter (0.80 and 1.55, bottom centre of table 2). Multiplicative models fitted using these two values for the interaction term produced bounds on conditional POC for HCV⁺ that are shown in figure 4 (right panel). The lower bound was essentially the same as that obtained from the mixture parameter, confirming that values of POC for radiation could be zero throughout the entire range of doses. The upper bound was quite high, reflecting the large degree of uncertainty in the POC estimate when there is concurrent HCV infection. This approach is not generally practical, however, because bounds on the interaction parameter are not relevant to the HCV⁻ dose response.

In summary, similar inference about POC was derived using the mixture model as was obtained in the previous section by examining the separate fits of the additive and multiplicative models. An advantage to the mixture model approach is that it does not require an assumption that the theoretical mechanism of biological interaction—multiplicative or additive, with or without interaction—is reflected in the data, which may be subject to the unadjustable effects of unmeasured factors. Furthermore, the impact of uncertainty, including uncertainty as to the form of the model, is described in a single POC estimate with bounds based on the profile likelihood of the mixture parameter, rather than by having to compare the results for different models, as was done in comparing the additive and multiplicative models displayed in figure 2.

5. Discussion and conclusions

There are two major reasons why radiation exposure should not be considered alone in determining probability of causation for radiation:

- (1) the magnitude of the background of disease occurrence attributable to non-radiation risk factors may impact the proportion of cases that are related to radiation, especially if these non-radiation risk factors play stronger roles than radiation in disease etiology;
- (2) non-radiation factors may confound the role of radiation or act synergistically with radiation.

Our results are inconclusive as to whether the joint effect of radiation and HCV infection on the occurrence of chronic liver disease is greater than additive and, thus, it is not clear whether there is biological interaction. This inconclusive result may reflect a lack of statistical power owing to few HCV⁺ persons who were heavily exposed to radiation, but it may also be partly due to other, unmeasured factors. If the best-fitting, slightly super-multiplicative model that was most consistent with these sparse data is the correct mechanistic model, both factors would act virtually independently from the point of view of POC, as demonstrated in figure 4. However, additive effects would result in a small POC for radiation in the presence of HCV infection because the relative risk of liver disease for HCV is much larger than for radiation. Further data are needed to resolve the mechanism of the joint effect.

When studies of the joint effect of radiation and other risk factors lack statistical power to reveal the precise mechanism of the joint effect, the calculated probability of causation based on a particular assumed model for the joint effect can be inaccurate if the model is wrong. Even if the model for the joint effect is mechanistically correct, it is unlikely to capture the myriad subtle effects that exist but cannot be practically controlled for in epidemiological studies. The true mechanism of joint effect would be an important consideration for calculating probability of causation if we had a precise risk model specific to a particular individual's spectrum of all relevant risk factors. Furthermore, in cases where a linear dose response is well known to hold, such as the linear excess relative risk of cancer mortality [26], the mixture model could distort the estimated POC because of its inherent nonlinearity. However, epidemiological data can only approximate the individual's overall spectrum of risk because it is not possible to control or adjust for all possible sources of heterogeneity. We therefore prefer the use of a more general model that does not force a choice between additivity and multiplicativity when that choice cannot be made reliably on theoretical grounds or based on the data.

The additive and multiplicative models used here are commonly used in applications involving POC, so the concepts and caveats we mention are equally relevant to other radiation related diseases and their associated risk factors. Some studies of joint effects (e.g. smoking and radon) utilised mixture models but rejected one or the other of the additive and multiplicative