表2　QUS測定値（骨密度1標準偏差値低下に対する骨折相対リスク，年齢・性調整）

	測定値	脊椎以外の骨折	臨床的脊椎骨折
QUS (A-1000plus)	SOS	NS	2.02* (1.09-3.77)
	BUA	1.63* (1.06-2.53)	1.73† (0.92-3.32)
	Stiffness	1.46† (0.95-2.28)	2.15* (1.10-4.28)
DXA (QDR-4500)	腰椎 BMD	NS	2.11* (1.16-3.98)
	大腿骨頸部	NS	NS

*: $p<0.05$　†: $p<0.1$

表3　QUS測定値と骨密度の骨折予知の比較
（1標準偏差低下に対する相対リスク，年齢・性調整）

	脊椎以外の骨折	臨床的脊椎骨折
SOS	1.23 (0.82-1.86) NS	1.79 (0.94-3.49) NS
腰椎 BMD	1.30 (0.90-1.93) NS	1.99 (1.11-3.75) *
BUA	1.88 (1.19-2.99) *	1.37 (0.69-2.76) NS
腰椎 BMD	1.04 (0.70-1.58) NS	2.01 (1.06-4.00) *
Stiffness	1.63 (1.03-2.61) *	1.78 (0.86-3.74) †
腰椎 BMD	1.13 (0.77-1.71) NS	1.86 (1.00-3.62) *

*: $p<0.05$　†: $p<0.1$　NS: 有意差なし

1　方　　法

対象集団は，放射線影響研究所において，1958年から2年に1回の健診で追跡調査している成人健康調査集団である。今回の解析の対象者は，1998～2000年の健診受診時に，超音波骨量測定（A-1000 plus）およびDXA（QDR-4500）による骨密度検査を受け，カルシウム・骨代謝に関連している薬剤を内服していた人を除いた2,434人（男750人，女1,684人，平均年齢69.0歳，52～97歳）である。ベースラインの対象者の特性は**表1**に示す。骨折発生は，2003年3月までの検診時において問診票で自己申告により骨折を調査した。解析は，ロジスティク回帰分析で解析した。

2　結　　果

追跡期間中，自己申告の脊椎骨折は19人（男2人，女17人），脊椎以外の骨折は40人（男17人，女33人）であった。年齢調整後，BUA, stiffnessは脊椎以外の骨折を予知したが，SOS，腰椎骨密度，大腿骨頸部骨密度は予知しなかった。BUA 1SD低下に対する脊椎以外の骨折の相対リスクは1.63（95%信頼区間1.06-2.53），stiffnessでは1.46（95%信頼区間0.95-2.28）であった。自己申告の脊椎骨折に対して，SOS，BUA，stiffness，腰椎骨密度は予知したが，大腿骨頸部骨密度は予知しなかった（**表2**）。SOS 1SD低下に対する脊椎骨折の相対リスクは2.02（95%信頼区間1.09-3.77），BUAでは1.73（95%信頼区間0.92-3.32）stiffnessでは2.15（95%信頼区間1.10-4.28），腰椎骨密度では2.11（95%信頼区間1.16-3.98）であった。

超音波骨量測定値と腰椎骨密度を同じ統計モデルに入れ，相対リスクを比較した（**表3**）。脊椎以外の骨折については，BUA，stiffnessは骨折を有意に予測したが，腰椎骨密度低下に対する相対リスクは正の値を示すものの有意ではなかった。脊椎骨折については，腰椎骨密度は骨折を予知したが，BUA，SOS，stiffnessは相対リスクが正の値を示すものの有意ではなかった。

3 考　　察

QUS 測定値と骨折との関係は，横断的あるいは症例・対照研究で，女性で大腿骨頸部，橈骨下端，脊椎骨折をもつ人は，もたない人に比べ BUA 値は 15～30%低い傾向にあり，BUA が 1SD 低下に対して脊椎骨折のオッズ比は 1.5～3 であった[1～3]。70～80 歳の 7562 人の女性を対象にした大規模な横断調査から，踵骨 QUS 測定値 1SD 低下あたり大腿骨頸部骨折のオッズ比は 2.1～2.7 倍であると報告されている[4]。縦断調査のシステマテック・レビューによると，BUA，SOS 1SD 低下による大腿骨頸部骨折リスクはそれぞれ 1.7～2.0 倍であった[5]。骨密度を考慮に入れても，相対リスクは変わらず，BUA や SOS は，骨密度とは独立して，骨折を予知した[6,7]。これらから，超音波測定値は，骨質に関する骨折リスクの一面を評価しているのではないかと考えられている。われわれの調査では，骨折を起こした人数が少ないため，QUS と骨密度を同時にモデルに入れると，脊椎以外の骨折は QUS 測定値，臨床的脊椎骨折は腰椎 BMD の有意性が残った。今後，追跡期間を延ばし骨折例を増やして，骨密度と QUS 測定値の骨折予知力に違いがあるのか，さらに検討する必要がある。

結　　論

2 年間の縦断調査から QUS 測定値，腰椎骨密度は，脊椎骨折あるいは脊椎以外の骨折を予知することを認めた。超音波骨量測定値と骨密度の予知力を比較すると，脊椎骨折においては，骨密度が，脊椎以外の骨折においては，BUA，stiffness がよりよく予知した。

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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

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

where $P(D|0)$ is the prevalence of disease not related to exposure, the background prevalence. $\mathrm{AF}(x)$ 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:

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

where $\mathrm{ERR}(x) = [P(D|x) - P(D|0)]/P(D|0)$ is the excess relative risk function, the relative risk [$\mathrm{RR}(x) = P(D|x)/P(D|0)$] 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,

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

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).

		Radiation dose (shielded kerma, Gy)									
		0		>0, ⩽1		>1, ⩽4		>4		All	
Factor	Level	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 $\geqslant 5$). 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 ($\mathrm{ERO}(v) = \gamma$ when $v = 1$) and the excess relative odds for radiation ($\mathrm{ERO}(x) = x\beta$, where β is the excess in the odds ratio per unit dose x, in Gray). An additive model for the joint effect is

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

and a multiplicative model is

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

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

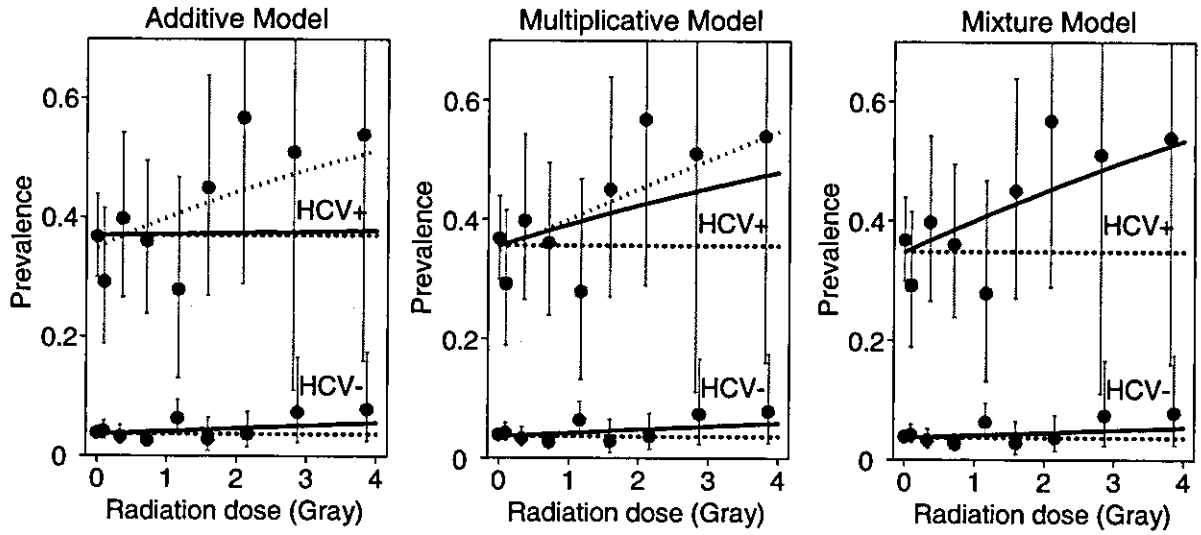

Figure 1. Prevalence of liver disease. Points are city-, gender-, and age-adjusted prevalences grouped by dose with 95% confidence intervals. Solid lines were derived from the models described in table 2 fit to individual (ungrouped) data. The horizontal dotted lines represent the background (no radiation 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 ($\alpha_{age\text{-}squared}$)	−0.0012	(−0.0022, −0.0003)	−0.0012	(−0.0022, −0.0002)	−0.0012	(−0.0022, −0.0002)
HCV (ERR_V)	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 $62\frac{1}{2}$ 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

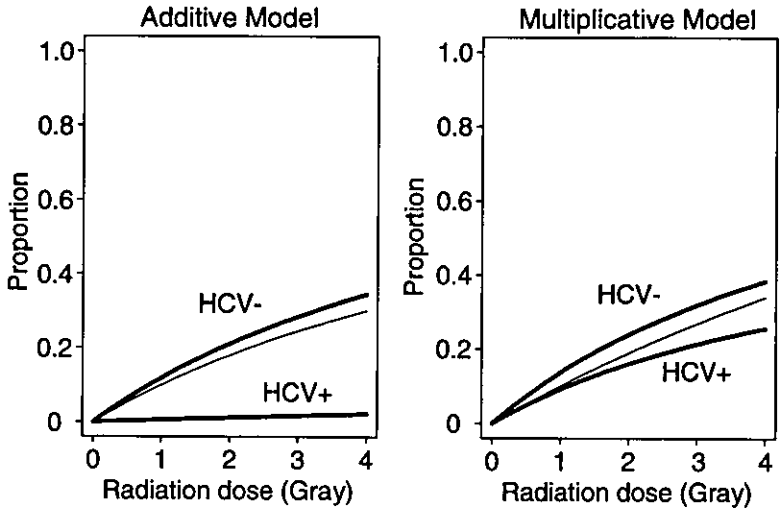

Figure 2. Probability of causation (POC) of liver disease for radiation estimated according to the additive or multiplicative model without statistical interaction. Estimates are conditional on HCV infection status. The baseline prevalence with no HCV infection and no radiation exposure ($P(D|0, 0)$; 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

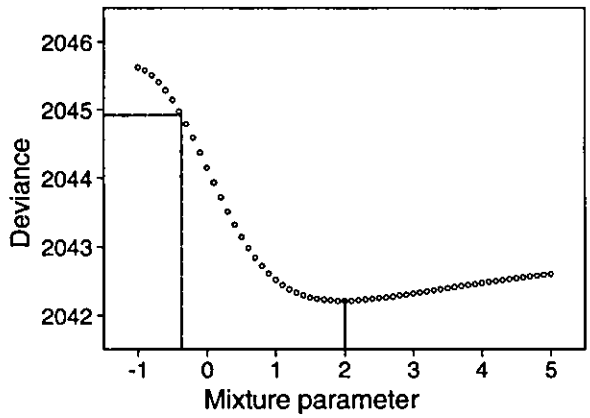

Figure 3. Estimation of the mixture-model mixture parameter by maximum profile likelihood. The best-fitting model was that with $\theta = 2.0$ (solid vertical line; minimum deviance = 2042.21). The one-sided 95% lower bound, −0.37, was derived as the point where the deviance increased by 2.706 (i.e.,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

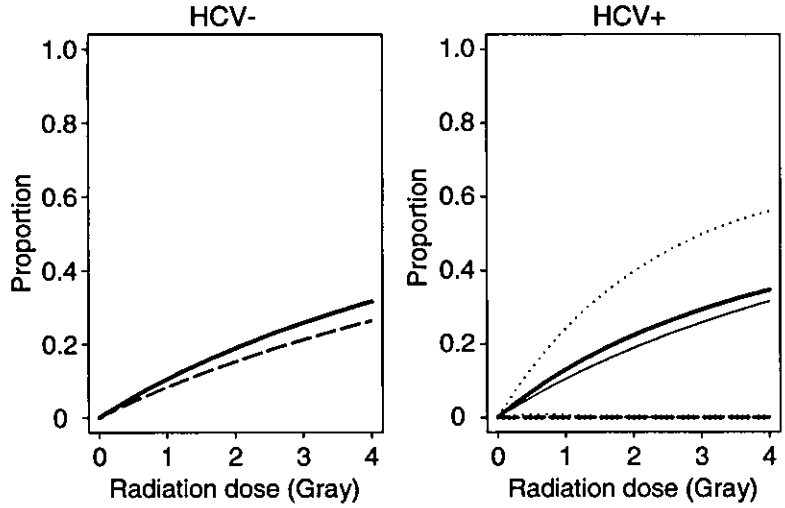

Figure 4. Probability of causation for radiation with the mixture model, conditional on viral infection status (solid curves). The dashed lines are the lower bounds on POC based on the profile likelihood for the mixture parameter. The dotted lines in the HCV^+ panel represent bounds on the POC derived 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

models and accepted the model scale that was not rejected [6]. Failure to reject one of these specific models is not equivalent to proving that it is the appropriate scale on which to model the joint effect (note that, in our example, neither model could be rejected). Mixture models may be more appropriate than the simpler additive and multiplicative models for some complex joint mechanistic effects. Linear dose responses are preferred in much radiation risk work, particularly with cancer; the mixture model results in a non-linear dose response even if the component parts are linear, unless the mixture parameter is zero or unity. Even if the hypothesised, underlying mechanism is of the simpler linear additive or multiplicative form, a mixture model may capture more complicated aspects of causality (due, for example, to confounders or effect modifiers) that are not explicitly measured. Such effects may lead to departure in the observed data from the trends expected to result from simple causal mechanisms. Given that these uncertainties will apply to the transport of POC from an epidemiological study to an individual regardless of what model is fitted, we therefore opine that it is better to base calculation of probability of causation on the joint effect actually manifest in the observed data in the face of such lurking effects than to base it on an estimate of joint effects based on a model that, even if theoretically correct, is not estimated correctly by the data in hand.

The idea that radiation POC is related to baseline risk conditional on other risk factors is not new. The US National Academy of Sciences Subcommittee that reviewed the draft update of the radio-epidemiological tables [27] pointed out an important implication for use of POC when absolute excess risk is the same in two populations with different baseline risks: 'In the high-baseline-risk population, the POC will be lower because it is more likely that the cancer was caused by factors other than radiation' (page 22). However, the idea of specifically accounting for risk factors that partly explain the baseline risk, and possibly interact with radiation in the etiology of disease, seems to be an area of research with much potential for development.

It is apparently common procedure to decide liability, not on the estimated POC, but on an upper confidence bound for the POC [5]. It can be argued that the existence of liability should be based on the POC point estimate itself because that is the best estimate obtainable from the available data. However, if bounds on the POC are desired to allow for a margin of error in deciding causation, it might be preferable to base the bound on a posterior probability (Bayesian) interpretation of the POC rather than on the frequency properties of confidence intervals. For applications in which a prior distribution over the parameter space can be specified, a Bayesian approach—unlike more traditional approaches—would allow for simple probabilistic interpretations on the uncertainties in POC.

Finally, the term 'probability of causation' may not make sense in the case of etiologic interaction, where responsibility is shared among the contributing agents. There are varied opinions regarding how to apportion risk from interaction [10]. If the joint effect is multiplicative, the classical assigned share for radiation based on excess relative risk is independent of the other, non-radiation risk factor. However, with statistical interaction there is some proportion of cases that might not have occurred even with radiation exposure had the other risk factor not been present. We condition on the other, non-radiation risk factor when calculating POC for radiation; thus, all excess risk associated with radiation is attributed to radiation although a portion of that risk may be due to the joint effect. Exposure to non-radiation risk factors may involve personal lifestyle choices or, as in the case of genetic factors, circumstances outside the exposed person's control. Whether to assign all of the joint causation to radiation, to the other factor, or to apportion them is a decision that must be made in each individual case of application of POC. It might therefore be useful for comparison to report, in addition to the conditional POC we recommend, an alternative POC for radiation calculated by

attributing all of the joint effect to the other, non-radiation, risk factor. Attributable fractions 'attributable to interaction' [28] are also being investigated in the POC setting.

Our recommendations regarding probability of causation can be summarised as follows.

- Exposure to risk factors other than radiation can be an important determinant of the role played by radiation in leading to disease and therefore cannot be ignored when assessing probability of causation for radiation.
- Mechanistic models for the joint effect of radiation and other factors, such as the additive and multiplicative models, might not adequately fit observed epidemiological data that are subject to lurking effects of unmeasured factors.
- When based on epidemiological data without well accepted theoretical mechanistic underpinnings, we recommend calculating probability of causation using a general, empirical model, which is less likely to be biased from untestable assumptions regarding the mechanisms that generated the actual, observed data.

Acknowledgments

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Appendix. Mathematical details

A model that fits the odds of disease as a joint function of radiation dose x and factor Z (taking value z) predicts the prevalence via

$$P(D|x,z) = \frac{f[P(D|x,z)]}{1+f[P(D|x,z)]} \tag{A.1}$$

where P is the probability of being diseased and $f(P) = P/(1-P)$ is the odds of disease. The probability of causation for radiation (POC) conditional on the value of z is based on the attributable fraction:

$$\mathrm{AF}(x|z) = \frac{P(D|x,z) - P(D|0,z)}{P(D|x,z)}. \tag{A.2}$$

Equation (4) of Seiler [29], though not defined as a conditional POC, is the same as this conditional POC, because what he calls the 'attributable relative risk for radiation' in the numerator is $P(D|x,z) - P(D|0,z)$ in the case of the additive model.

With the additive excess-relative-risk model used to derive the assigned shares in follow-up studies, defining POC from the basic definition of conditional attributable fraction (equation (A.2)) produces the same estimate as that for assigned shares based on the formula for conditional excess relative risk [5]:

$$\begin{aligned}\mathrm{AF}_{\mathrm{add}}(x|z) &= \frac{P(D|x,z) - P(D|0,z)}{P(D|x,z)} = \frac{\mathrm{ERR}_x}{1+\mathrm{ERR}_z+\mathrm{ERR}_x} \\ &= \frac{\mathrm{ERR}_x/(1+\mathrm{ERR}_z)}{1+\mathrm{ERR}_x/(1+\mathrm{ERR}_z)} = \frac{\mathrm{ERR}_{x|z}}{1+\mathrm{ERR}_{x|z}} = \mathrm{AS}_{x|z},\end{aligned}$$

where, for notational simplicity, we write the excess relative risk function $\mathrm{ERR}(x)$ as ERR_x, ERR_z is similarly the excess relative risk for factor Z, $\mathrm{ERR}_{x|z}$ is the excess relative risk for exposure to x given z, and AS represents *assigned shares*. In other words, calculating POC from basic principles is equivalent to using the more familiar AS formula when the disease risk (incidence or prevalence) is directly modelled using the relative risk. Similar formulae can be derived for the multiplicative and mixture models based on the ERR:

$$\mathrm{AF}_{\mathrm{mult}}(x|z) = \frac{\mathrm{ERR}_x}{1+\mathrm{ERR}_x} = \mathrm{AS}_x$$

$$\mathrm{AF}_{\mathrm{mix}}(x|z) = 1 - \frac{1+\mathrm{ERR}_z}{[(1+\mathrm{ERR}_x)(1+\mathrm{ERR}_z)]^{\theta}[1+\mathrm{ERR}_x+\mathrm{ERR}_z]^{1-\theta}}.$$

In the case of cross-sectional studies estimating the disease prevalence via the odds, as was done in the present work, the attributable fraction is

$$\mathrm{AF}^{\mathrm{O}}(x|z) = \frac{P(D|x,z) - P(D|0,z)}{P(D|x,z)} = 1 - \frac{\left\{\frac{f[P(D|0,z)]}{1+f[P(D|0,z)]}\right\}}{\left\{\frac{f[P(D|x,z)]}{1+f[P(D|x,z)]}\right\}}$$

(the superscript 'O' on AF stands for 'odds'). One can always compute the POC directly using equation (A.2) once a model for $P(D|x,z)$ has been fitted. Alternatively, we can derive formulae for POC analogous to those based on the ERR by substituting the appropriate model for $f(P)$ and solving algebraically in terms of the excess relative odds, ERO. Writing $f[P(D|0,0)]$ as f_0, $\mathrm{ERO}(x)$ as ERO_x and $\mathrm{ERO}(z)$ as ERO_z, the equations for attributable fractions for the odds models become

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{add}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{1+\mathrm{ERO}_x+\mathrm{ERO}_z} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mult}}(x|z) = 1 - \frac{\frac{1}{1+\mathrm{ERO}_x} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

and

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mix}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{[(1+\mathrm{ERO}_x)(1+\mathrm{ERO}_z)]^{\theta}\times[1+\mathrm{ERO}_x+\mathrm{ERO}_z]^{1-\theta}} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)}.$$

To evaluate these three formulae, we can write them generally as

$$\mathrm{AF}(x|z) = 1 - \frac{a(x) + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

where, assuming ERO_x is an increasing function of x, $a(x) \leqslant 1$. Furthermore, $\mathrm{AF} = 0$ [$a(x) = 1$] when $x = 0$ ($\mathrm{ERO}_x = 0$) and AF increases as ERO_x increases.

Statistical interaction terms may be appended to the additive (text equation (4)) and multiplicative (text equation (5)) models to examine departure from those specific models. The additive model with interaction is

$$f[P(D|x,z)] = f[P(D|0,0)](1+\mathrm{ERO}_x+\mathrm{ERO}_z+\Delta xz), \tag{A.3}$$

and the multiplicative model with interaction is

$$f[P(D|x,z)] = f[P(D|0,0)][(1+\mathrm{ERO}_x)(1+\mathrm{ERO}_z)]\mathrm{e}^{\delta xz}, \tag{A.4}$$

where, in the presence of HCV infection, Δ is the incremental difference in the excess relative odds per unit difference in dose and e^{δ} is the relative change in the odds ratio (δ is the logarithm of the relative change) for a unit difference in dose. The attributable fractions corresponding

to these two interaction models are easily derived and equivalent to those above, except that the $a(x)$ terms include the full joint-effect risk model with interaction:

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{add,int}}(x|z) = 1 - \frac{\frac{1+\mathrm{ERO}_z}{1+\mathrm{ERO}_x+\mathrm{ERO}_z+\Delta xz} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)},$$

and

$$\mathrm{AF}^{\mathrm{O}}_{\mathrm{mult,int}}(x|z) = 1 - \frac{\frac{1}{(1+\mathrm{ERO}_x)\times(1+\mathrm{ERO}_z)\times e^{\delta xz}} + f_0(1+\mathrm{ERO}_z)}{1+f_0(1+\mathrm{ERO}_z)}.$$

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カレントテラピー

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危険因子の民族差

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abstract

骨密度は民族間に差があり，最も高いのが黒人で，次に白人，アジア人の順である．骨粗鬆症の危険因子として，年齢，性，体重，閉経，カルシウム摂取，運動，喫煙，カフェイン過剰摂取，アルコール過剰摂取など多くの因子が挙げられ，これらの危険因子は民族間で共通したものであり，頻度あるいは平均値は民族間で違う．しかし，民族間にみられる骨密度の差は，体重やライフスタイルなどを調整すると小さくなり，各危険因子が骨粗鬆症に寄与する割合は民族間でほぼ同じと考えられる．骨折発生率も民族間に差があるが，年齢，低骨密度，骨折既往は共通な危険因子である．骨密度，既存骨折は欧米白人と日本人においてほぼ同程度に将来の骨折を予測し，これらの危険因子の骨折予測能力には民族差はないと考えられる．

I はじめに

骨密度が最も高いのは黒人で，次に白人，アジア人の順である．骨折の頻度を比較すると，日本人の脊椎骨折の発生率は欧米白人に比べて約2倍高く[1]，大腿骨頸部骨折，上腕骨近位骨折，橈骨下端骨折の発生率は，北欧の約1/2程度であり，香港の中国人とほぼ同じである[2]．このように，骨密度，骨折の発生率には民族差があることはよく知られているが，それに関与する危険因子に民族差があるのか，これらの危険因子が骨粗鬆症，骨折発症の予測能力に差があるのかについてレビューしていきたい．

II 骨粗鬆症の危険因子の民族差

骨粗鬆症の危険因子として，年齢，性，体重，閉経，カルシウム摂取，運動，喫煙，カフェイン過剰摂取，アルコール過剰摂取など多くの因子が報告されている．これらの危険因子は，どの民族においても共通に認められるものであり，各民族における平均値や頻度は異なっている．例えば，アジア人は白人に比べ体重，カルシウム摂取量は少ないなどである．

しかし，これらの危険因子が骨密度に寄与する割合に民族差はあるのであろうか．ヨーロッパ系，アフリカ系，ヒスパニック系，アジア系アメリカ人を対象にしたいくつかの調査で，体格あるいはライフスタイルを調整することで，人種間の骨密度の違いの一部あるいは大部分を説明できると報告されている[3)~5)]．危険因子のなかで特に影響力が大きいのは

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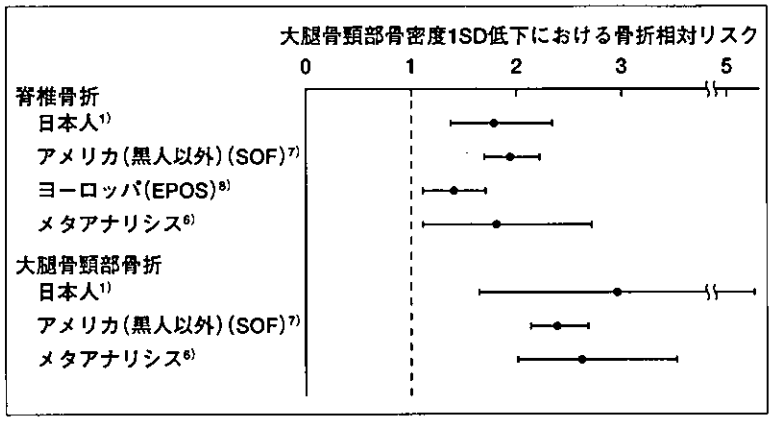

図1
骨密度による骨折リスク予測（民族間の比較，女性）
SOF：Study of Osteoporotic Fractures
EPOS：European Prospective Osteoporosis Study

体格で，体格のみ調整することで民族間の骨密度の差が消失したという報告もある[4]．このことは，民族間で平均体重に差はあるが，単位当たりの体重が骨密度に与える影響は民族間でほぼ同じであることを示している．最近の報告[3]では，アメリカに住む白人，フィリピン系，ラテンアメリカ系閉経後女性の骨密度の差は，体格，エストロゲン使用，カルシウムサプリメント使用，喫煙，飲酒，運動を調整すると小さくなり，これらの因子で骨密度の散らばりの20～40%が説明できるとしている．

III 骨折危険因子の民族差

1）低骨密度

骨密度が将来の骨折の重要な予測因子であることは，多くのコホート調査から明らかになっている．橈骨下端，踵骨，椎体，大腿骨近位のどの部位の骨密度も，将来の骨折リスクを予測でき，ベースラインでの骨密度が1標準偏差（SD）低いと，脊椎骨折の相対リスク（relative risk：RR）は1.7～2.4，大腿骨頸部骨折のRRは1.6～2.6，橈骨下端骨折のRRは1.4～1.7，全骨折のRRは1.4～1.6である[6]．これらの調査のほとんどは白人高齢女性を対象にしている．

アジア人を対象に，骨密度と骨折リスクを縦断的に検討した調査は，今のところ著者らの日本人コホートを約4年間追跡した調査[1]のみである．ベースライン腰椎骨密度が1SD低いと脊椎骨折は1.5倍となり，大腿骨頸部骨密度が1SD低いと脊椎骨折は1.8倍となった．大腿骨頸部骨折については，腰椎骨密度が1SD低いと1.4倍，大腿骨頸部骨密度が1SD低いと2.9倍であった．図1に日本[1]，アメリカ[7]，ヨーロッパ[8]，メタアナリシス[6]での骨密度による骨折リスク予測結果を比較している．どの調査も骨密度1SDの絶対量はほぼ同じ値を示していて，骨密度1SD当たりの骨折予測能力は，日本人と欧米白人に大きな差はないと考えられる．

2）既存骨折

既存骨折も将来の骨折の決定因子である．1966年から1999年までに発表された文献のメタアナリシスの結果[9]では，既存骨折があると，そうでない人に比べ将来の骨折リスクは約2倍，既存脊椎骨折があると将来の脊椎骨折は4倍であった．この解析結果は，骨密度は考慮に入れられていないが，最近の多くの調査から，骨密度を調整しても，既存骨折は将来の骨折の重要な危険因子となることが明らかになっている．これは，既存骨折は，単に低骨密度を反映しているだけでなく，骨の微細構造の欠陥，転倒しやすさ，転倒したときに骨折を防ごうとする反射的な行動能力の低下のサロゲートマーカーとなっていると考えられる．ヨーロッパで行われた調査（European Prospective Osteoporosis Study：EPOS）[8]で，年齢，性，腰椎骨密度を調整すると，既存脊椎変形がある人は，将来の脊椎骨折リスクは，2.9倍（95%信頼区間：1.7～5.1）で，著者らの日本人集団においては，年齢，腰椎骨密度を調整すると，既存脊椎骨折があると将来の脊椎骨折のリスクは女性では2.9倍（95%信頼区間：2.0～4.3）とほぼ同じRRを示した．既存骨折は，白人，日本人に共通した将来の骨折の大きな予測因子であり，その予測能