Cancer:
Misfortune or Carelessness?

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Preliminaries

- This does not represent a substantive research project: a letter to the editor of *Significance* was converted to an 'in-brief' article, and now this presentation is a slightly expanded version of that article.

- Caveat: I am going to talk about carcinogenesis, a process I know very little about

- In fact, the subject of this presentation is how to think about processes we know very little about

Models and Modelling

- A model is a substitute for reality
- Humans deal with reality by way of models
  - at a low level, as in vision
  - at a high level, as in planning
  - very explicity, as in a proportional hazards model
  - very vaguely, as in a half-formed mental picture
- a model of statistical consultancy: the statistician and the client (eg clinician) align their models

Models have consequences: driving

- Our model of the world affects the decisions we make
  - somebody whose 'model' of the A14 is an empty road will start their journey later than than somebody whose 'model' is that of continuous traffic jams

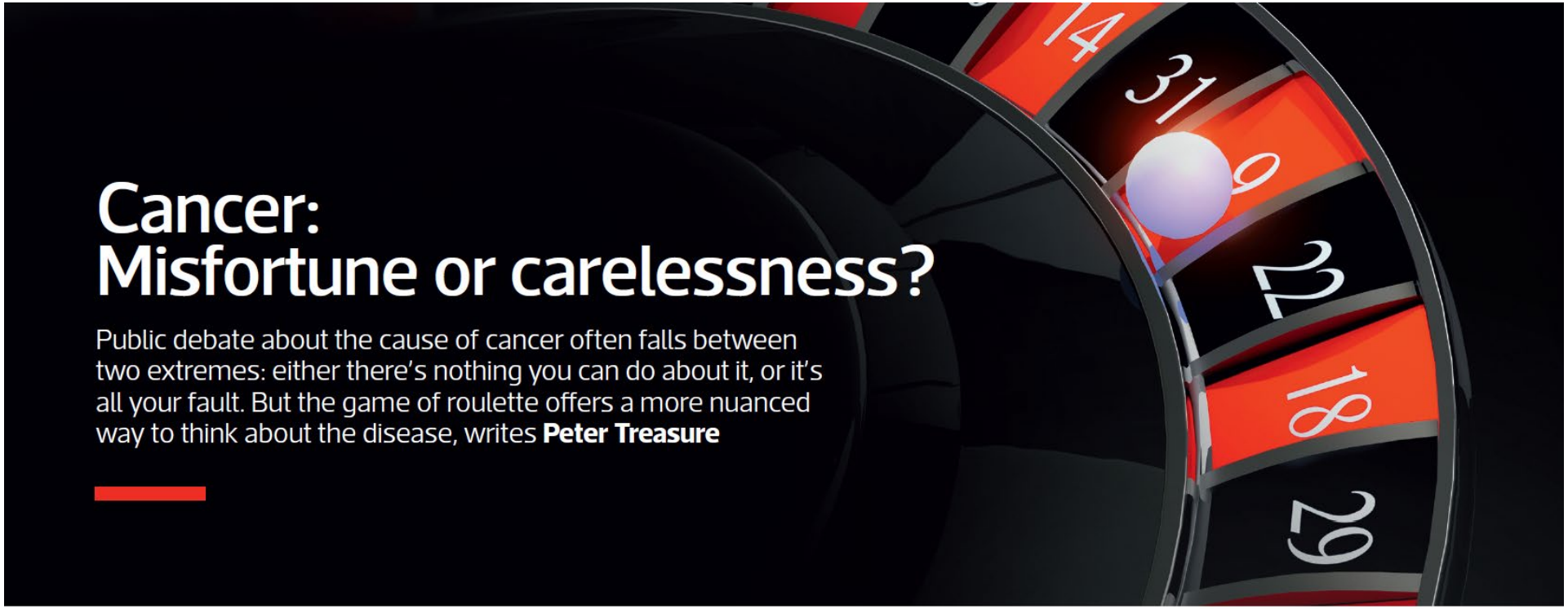
- To change someone's behaviour, change their model
  - an objective of a speed awareness course is to change the attendee's model of stopping a car from reducing speed to reducing kinetic energy

Models have consequences: carcinogenesis

- I shall talk about how our internal models of carcinogenesis may affect our behaviour, and therefore may affect our chances of getting cancer

- a smoker who reckons they are good for 100000 cigarettes before they get lung cancer is less likely to give up smoking than a smoker who sees each cigarette as having a small but finite chance of causing a malignancy

- is a glass of red wine 'liquid sunshine' or a flavoured solution of ethyl alcohol?



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Plan

1) describe some lay attitudes (=models) to the chances of getting cancer

2) present some analogies (=models) proposed by statisticians, intended to be more useful than the lay models

(an *analogy* of carcinogenesis is a model of carcinogenesis mapped onto a model, more familiar, of another process – retaining the essential features)

3) present my own analogy

('more useful' and 'essential feature' relate to changing behaviour for the better)

Lay Attitudes

Deterministic Models

- An individual might think that they will *certainly not get* cancer
  - magical thinking – bad things happen to other people
  - sometimes specific – "because I never smoked, I won't get lung cancer"

- An individual might think that they will *certainly get* cancer
  - sometimes almost certain, if the individual has inherited particular genes
  - true, if the individual lives long enough

- yes/no is not enough, we need 'when' as well

Choice Models

- Examples:
  - if you stop smoking you won't get cancer
  - if you sunbathe you will get cancer
  - if you have positive thoughts about your body you won't get cancer
  - ...

- It's ALL YOUR FAULT

- Randomness is missing

(Too) Random Models

- Pre-destination
  - "either I'm going to get cancer, or not get cancer, I don't know what cards I was dealt at birth, there is nothing I can do about it"

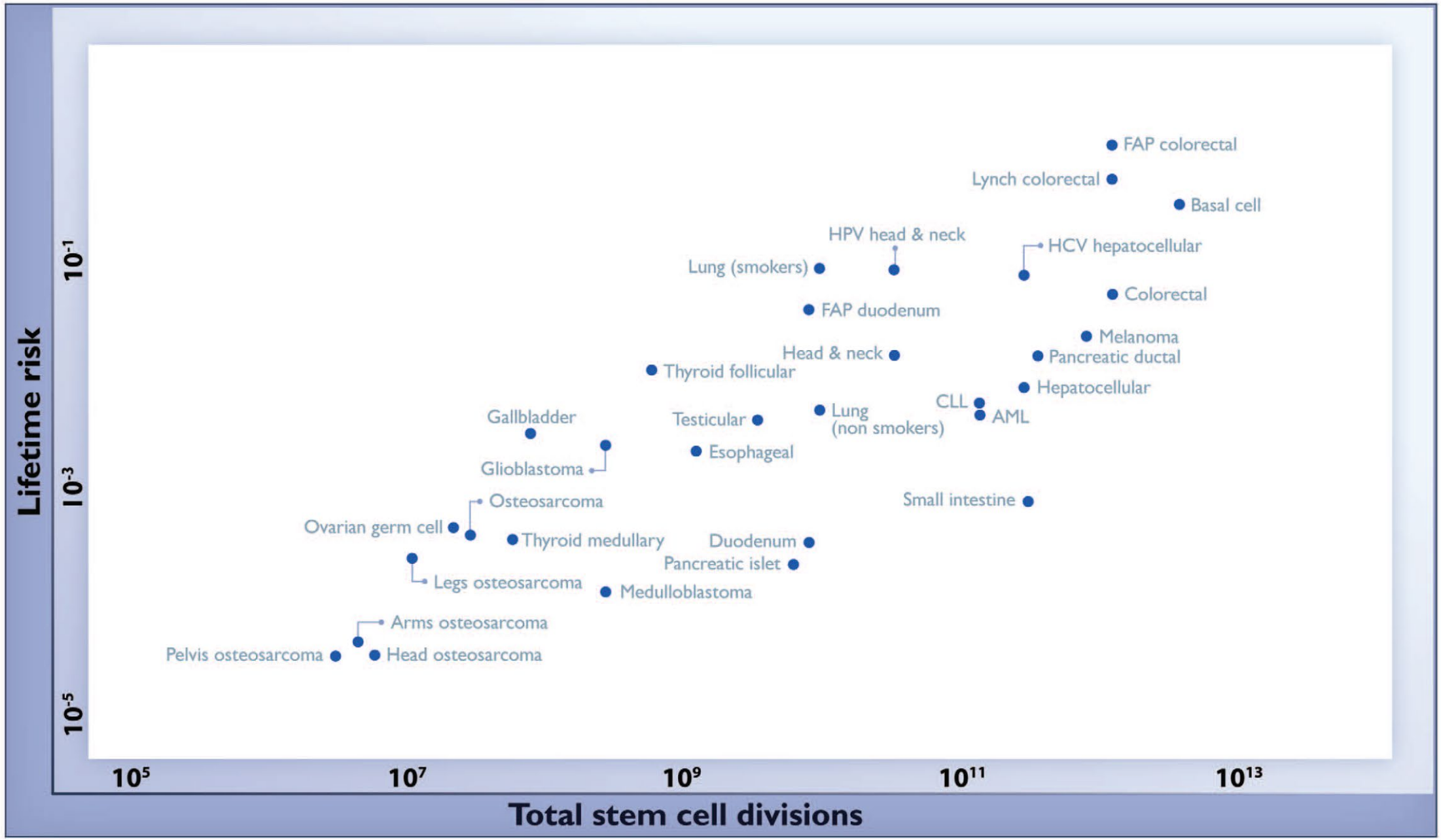
- Bad luck
  - "getting cancer is like the National Lottery in reverse, it's just bad luck if sooner or later your numbers get drawn , there is nothing I can do about it"

Statistical Analogies

Tomasetti and Vogelstein (2015)

- demonstrated that the lifetime risk of cancer for a particular body tissue is strongly associated with the number of stem cell divisions in that tissue
  - a phenomenon over which we have no control

- accompanying press release: "'Bad luck' of random mutations plays predominant role in cancer, study shows"



FAP = Familial Adenomatous Polyposis ◆ HCV = Hepatitis C virus ◆ HPV = Human papillomavirus ◆ CLL = Chronic lymphocytic leukemia ◆ AML = Acute myeloid leukemia

Fig. 1. The relationship between the number of stem cell divisions in the lifetime of a given tissue and the lifetime risk of cancer in that tissue.

Cancer News

The latest news, analysis and opinion from Cancer Research UK

Search News

Science & Technology | Health & Medicine | Personal Stories | Policy & Insight | Charity News | For Researchers | For Supporters

Health & Medicine

Cancer 'mainly bad luck'? An unfortunate and distracting headline

by Henry Scowcroft | Analysis
5 January 2015

49 comments

CRUK quote Spiegelhalter

In his response to the media stories, Professor Spiegelhalter had this excellent analogy:

> [Imagine] there are tickets in a bucket marked cancers of different types, and a lot of blank tickets (and some marked 'run over by bus' etc). Smoking means you might get 20 times as many 'lung-cancer' tickets, but you still may be lucky and not draw one: many smokers don't get lung cancer.
>
> So chance plays a very strong role, even in so-called preventable cancers. This leads to the apparently paradoxical observation that most lung cancers are 'caused' by smoking, while all lung cancers are also a matter of bad luck.

Cancer: What's luck got to do with it?

Recent press reports would have you believe that cancer develops randomly, and healthy living makes little difference. But that is a gross misinterpretation of a recent scientific paper, as Joseph E. Lucas and Guillermo Sapiro explain

Lucas and Shapiro (2015)

- Article in Significance: "Cancer – What's luck got to do with it?"
- They summarise the popular interpretation of Tomasetti and Vogelstein as

  > cancer develops randomly and [therefore] healthy living makes little difference

- and describe that model of carcinogenesis as "catastrophic and pessimistic"

Tomasetti and Vogelstein: Response

- T & V constructed a driving analogy as a response to criticism of their stem cell division model

Life	Road Journey
diagnosis of cancer	having an accident
# of stem cell divisions	length of journey
genes	mechanical condition of car
environment	road conditions
behaviour	driving style

- with a high correlation between length of journey (# of stem cell divisions) and having an accident (diagnosis of cancer)

T & V analogy: any good?

- Their road journey analogy …

  though ingenious, especially the notion of changing driving style affecting the chances of an accident

  … does not provide a natural way to incorporate a randomness modifiable by genes, environment, behaviour

- They end up making statements such as

  "Using this analogy, we estimate that two-thirds of the risk of getting into an accident is attributable to the length of the trip"

  Which were interpreted in the popular press as

  "Only one third of cancers have a cause … The rest are just bad luck"

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Science & Technology Health & Medicine

Reports that cancer is 'mainly bad luck' make a complicated story a bit too simple

Cancer Research UK response to T & V

- "[The view] that cancer is 'mainly bad luck' make[s] a complicated story a bit too simple"

- They were concerned that people may conclude that "there's nothing they can do to stack the odds in their favour" ...

  ... but "more than 4 in 10 cancers could be prevented"

- A better analogy is required

CRUK: Vase Analogy

- CRUK presented an analogy for carcinogenesis involving a vase falling off a shelf

Life	Vase
diagnosis of cancer	smashing on floor
mutating cancerous cells	the fall
environment	vase being pushed
behaviour	vase being pushed
preventing cancer	removing the push
preventing cancer	catching the vase

Tumour Roulette

Modifiable Stochasticity: Roulette

- Repeated spinning of a roulette wheel:
  - generates *random* numbers nearly all are 'innocuous' but some are 'bad'
    - 'bad' in the sense of representing a step on the the path to malignancy,
    - 'bad' in the sense of achieving malignancy
  - mimics the passing of *time* by the repeated spinning
    (once per day is a good way to think about it)
- The 'bad' numbers have to occur in the right order
  - cf Armitage-Doll multi-stage theory
- Changes in lifestyle or environment can be accounted for by *modifying* which numbers are 'bad'

Model 0

Imagine a roulette wheel with a thousand numbered pockets about its circumference. Each spin of the roulette wheel corresponds to a new day. Certain pockets, at certain times, represent a “bad” event. Five bad events in a defined order are needed for a particular cancer. An example would be:

$$\{610\} \rightarrow \{238\} \rightarrow \{165\} \rightarrow \{168\} \rightarrow \{693\}$$

which indicates that the first bad event occurs the first time the ball lands on 610, the second when it lands on 238 after the first bad event occurs, and so on, up to malignancy occurring when the ball lands on 693 after the fourth bad event.

Model 1

It is unrealistic for all bad events to have the same probability, so the model is revised such that a bad event may also occur if the ball settles in one of several pockets. The example is now:

$$\{610\} \rightarrow \{238\} \rightarrow \{165 \text{ or } 166\} \rightarrow \{\text{multiple of } 42\} \rightarrow \{693\}$$

In this example the probability per spin of the third bad event is twice that of the first two events, and the fourth bad event has an even higher probability.

Model 1a

Suppose, for example, that a lifestyle choice is known to hasten markedly the development of a cancer. The required sequence of events could look like:

$$\{610\} \rightarrow \{238\} \rightarrow \{165\} \rightarrow \begin{array}{l} \textit{If lifestyle = Y then} \\ \{\text{multiple of 2}\} \\ \textit{otherwise} \\ \{\text{multiple of 42}\} \end{array} \rightarrow \{693\}$$

where *Y* symbolises a detrimental behaviour such as smoking. Note that if a person changes their lifestyle for better (or worse), then the roulette wheel changes such that the number of bad pockets decreases (or increases).

Model 1b

Similarly, if a congenital genetic mutation *Z* means that the second bad event need not occur, then the sequence of events can be pictured as:

{610} → *If congenital mutation Z is present then* → {165} → {multiple of 42} → {693}
omit 2nd event
otherwise
{238}

Tumour Roulette: analogy table

Life	Roulette
passage of time	repeated spins of the wheel
cellular mutation	ball landing in a 'bad' pocket
malignancy	over a long series of spins, a set of 'bad' pockets is occupied in a particular order
effect of genes, environment, behaviour	number of 'bad' pockets
changing environment or behaviour	pockets converting from 'bad' to 'innocuous' or vice-versa

The Carcinogenesis Roulette Analogy

The Roulette Analogy incorporates

randomness …

… modifiable …

… over time

and features

an irreducible component of bad luck

an opportunity to shift the odds in your favour

providing a simple, realistic and useful model of how we get cancer

Thank You