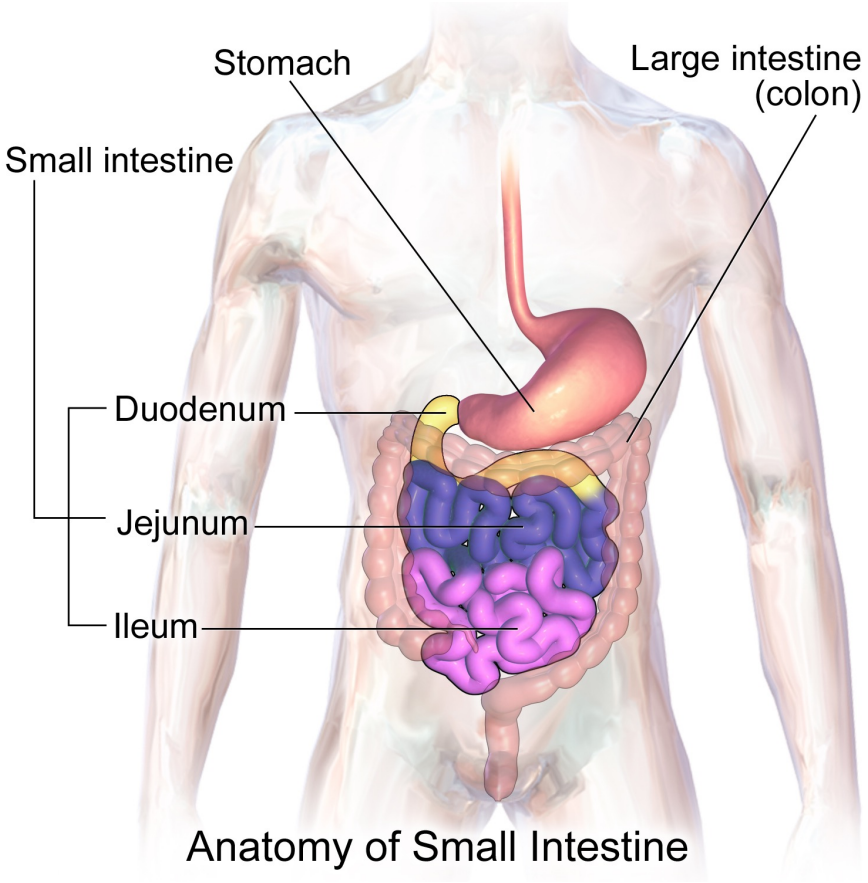
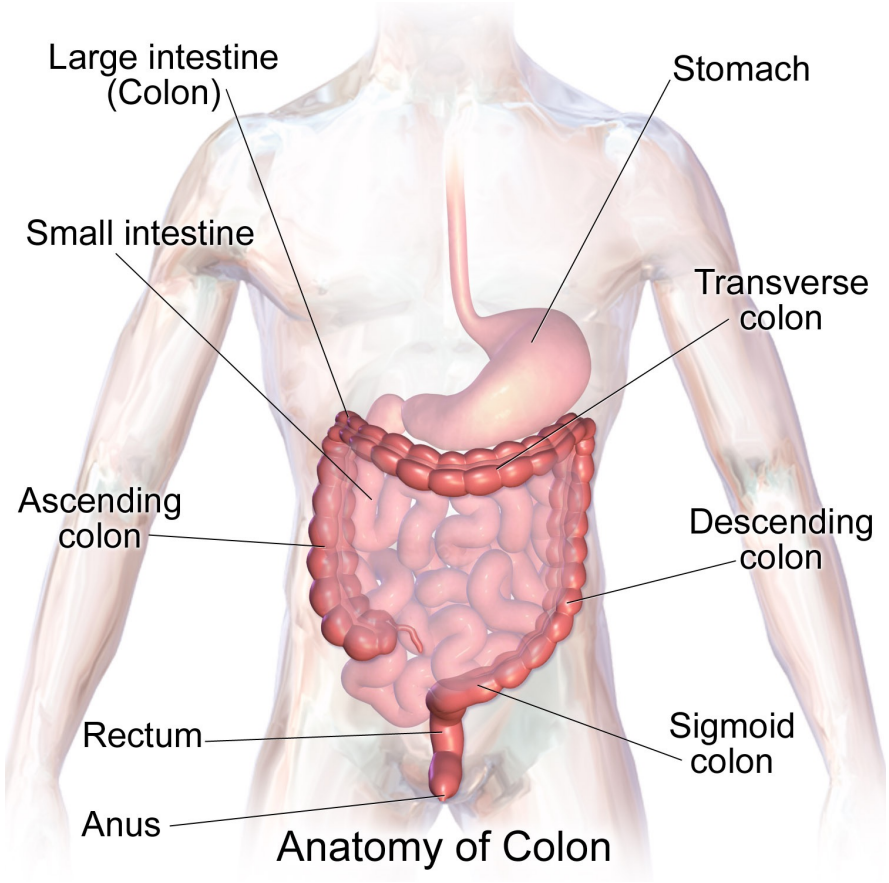
Mulstistage model of colorectal cancer, a simple mathematical model

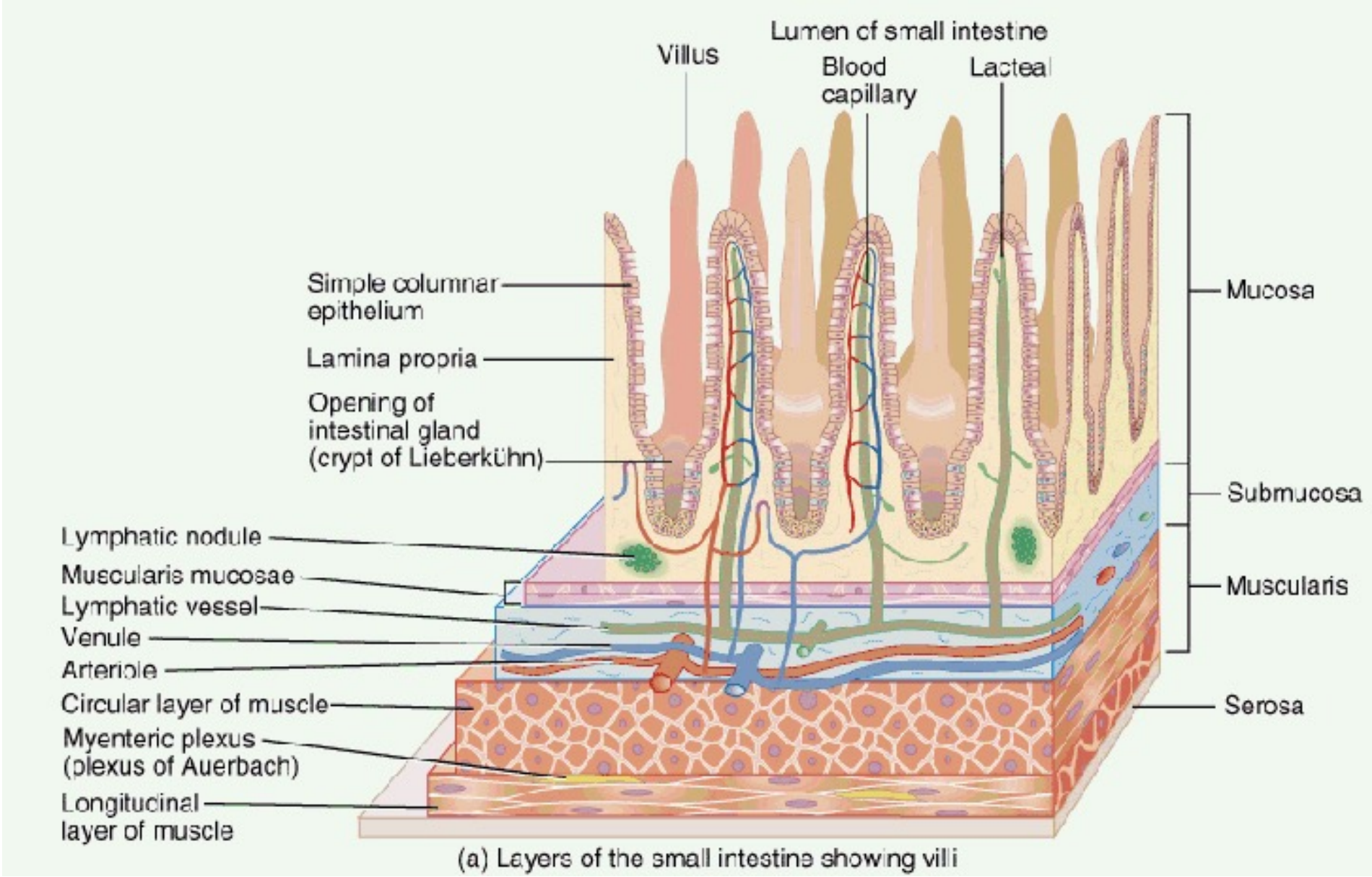
from Calabrese and Shibata: *A simple algebraic cancer equation: calculating how cancers may arise with normal mutation rates*, BMC Cancer 2010, 10:3

Mulstistage model of colorectal cancer

The human intestine







(a) Layers of the small intestine showing villi

$$p(\text{onset of illness at age } a) \approx b\,a^{k}$$

this constant incorporates all the biological parameters

number of stages

In the epidemiology of colorectal cancer, $k \approx 5$ or 6

Normal mutation rate is low, ~ 10^{-9} per base, per division.

This means that in a 1000 base-long gene, the mutation rate is $u \approx 10^{-6}$ per division.

Then the probability that in *d* divisions the gene is not mutated, is

$$p(\text{no mutation in gene}) \approx (1-u)^d$$

and therefore, the probability that it is mutated is

$$p(\text{gene is mutated})$$

$$= p(\text{at least one mutation in gene}) \approx 1-(1-u)^d$$

Then, if there are *N* compartments with *m* cells each that are at risk of reaching the critical mutation level, the probability that no cell reaches this critical level is

$$p\left(\begin{array}{l}\text{no cell in the } N \text{ compartments}\\ \text{reaches the critical level}\\ \text{of mutations}\end{array}\right)=\left\{1-\left[1-(1-u)^{d}\right]^{k}\right\}^{Nm}$$

and finally, the probability of the onset of illness is

$$p\left(\text{onset of illness after } d \text{ divisions}\right)=$$

$$=p\left(\begin{array}{l}\text{at least one cell in the } N\\ \text{compartments reaches the}\\ \text{critical level of mutations}\end{array}\right)=1-\left\{1-\left[1-(1-u)^{d}\right]^{k}\right\}^{Nm}$$

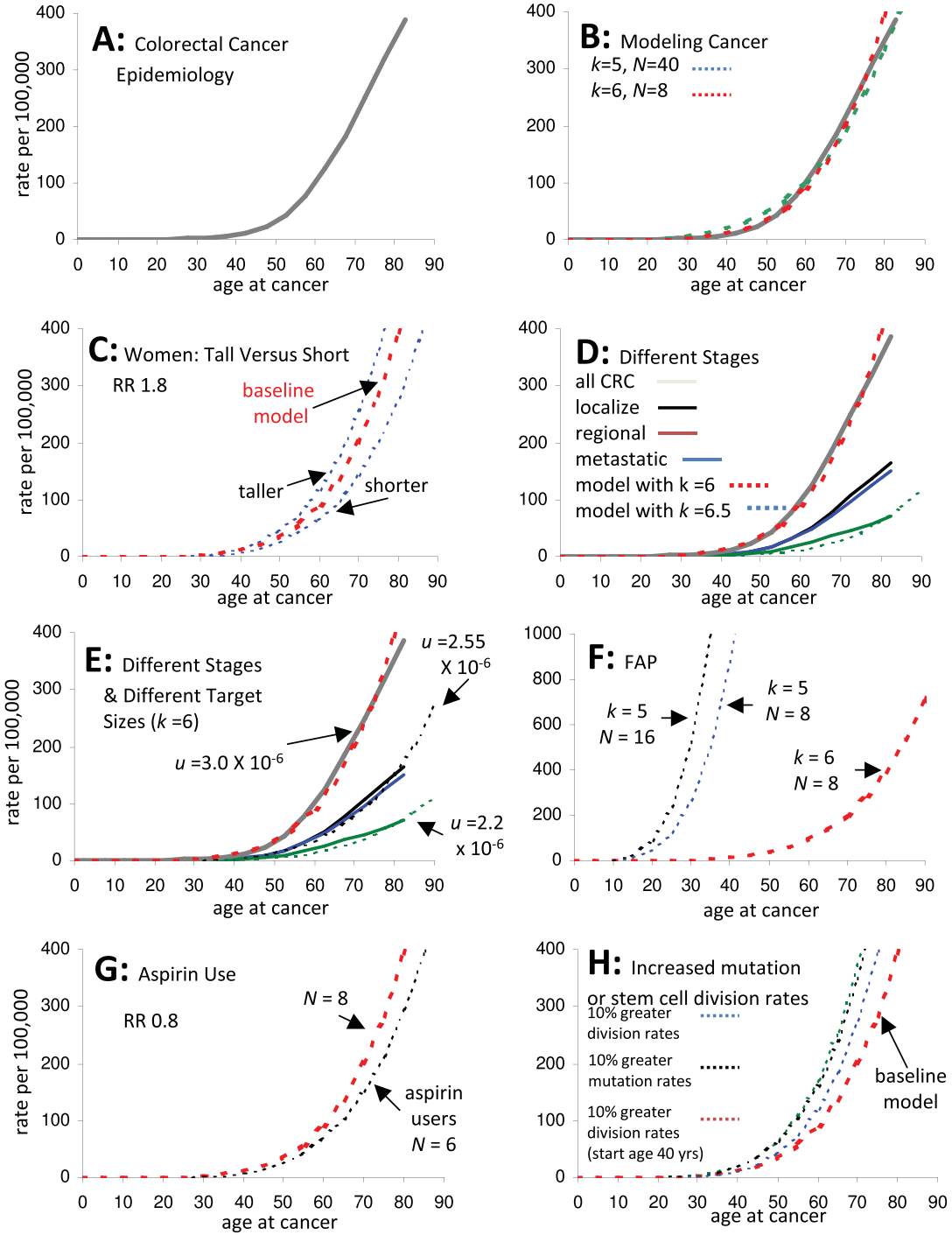
$$p\left(\text{onset of illness after } d \text{ divisions}\right) = 1 - \left\{1 - \left[1 - \left(1-u\right)^{d}\right]^{k}\right\}^{Nm}$$

$$\approx 1 - \left\{1 - \left[du\right]^{k}\right\}^{Nm}$$

$$\approx Nm\left(du\right)^{k}$$

Since $d \approx a/T$ (where T is the duplication time)

$$p\left(\text{onset of illness at age } a\right) \approx Nm\left(\frac{a}{T}u\right)^{k} = \left(\frac{Nmu^{k}}{T^{k}}\right)a^{k} = ba^{k}$$



from P.Calabrese and D. Shibata, "A simple algebraic cancer equation: calculating how cancers may arise with normal mutation rates", BMC Cancer **10** (2010) 3

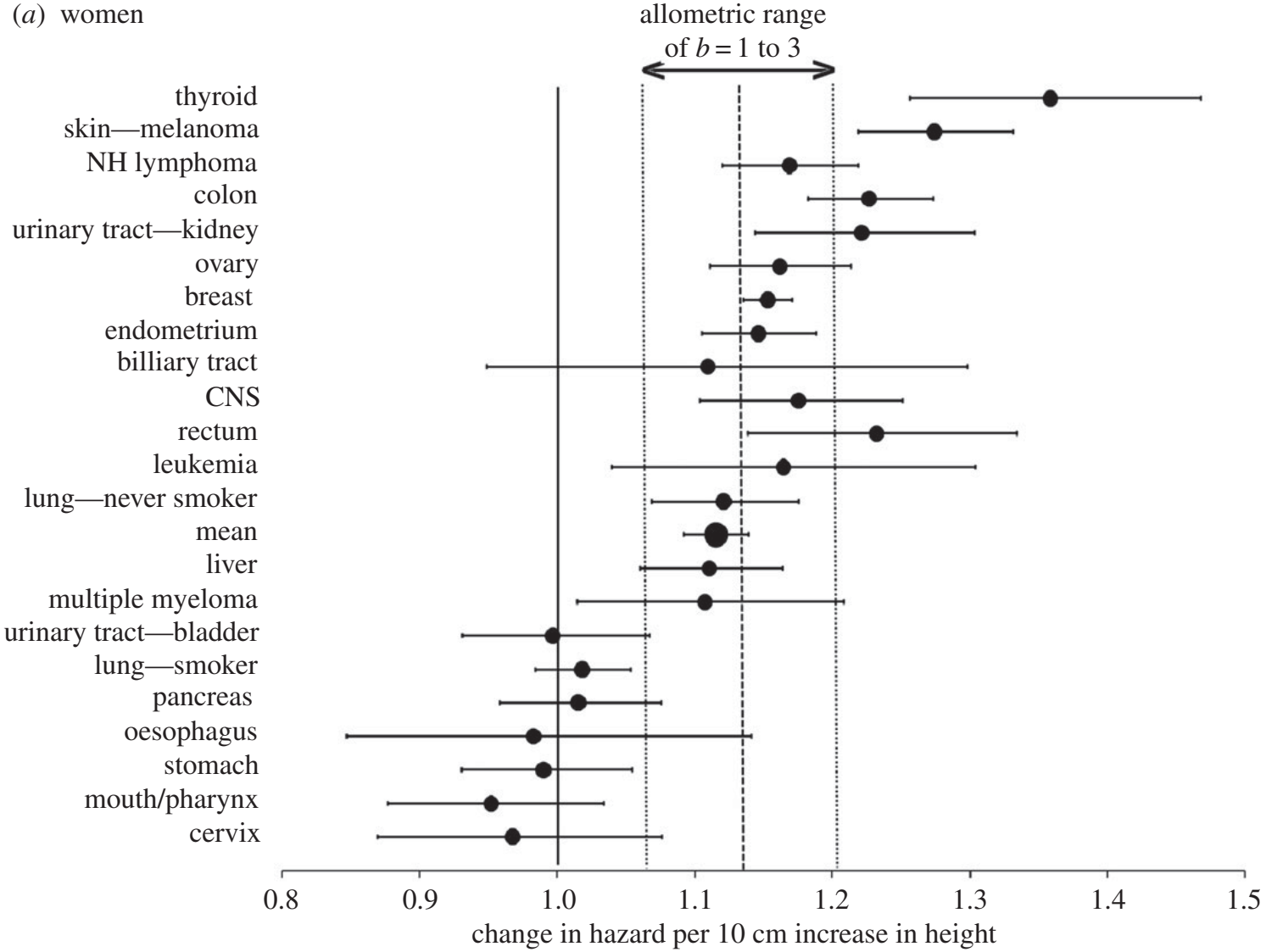


Figure 2. A comparison of the observed and predicted effect of height on the risk of specific cancers: the observed hazard ratio (HR_{10}) and 95% confidence interval linking a 10 cm increase in height to the increased risk of specific cancers, showing only cancers included in at least two of the target studies (for women [22–25]; for men [23–25]). The vertical lines illustrate: no effect of height ($HR_{10} = 1.00$; solid line); the average HR_{10} predicted from the multistage model based on the allometry of human height to overall body mass, which is used as a proxy for cell number (dashed line); and (3) the predicted effect based on the expected extremes of organ cell number allometry to height: linear, $b = 1$ (lower dotted line); and volumetric, $b = 3$ (upper dotted line). For data sources, see electronic supplementary material, table S1.

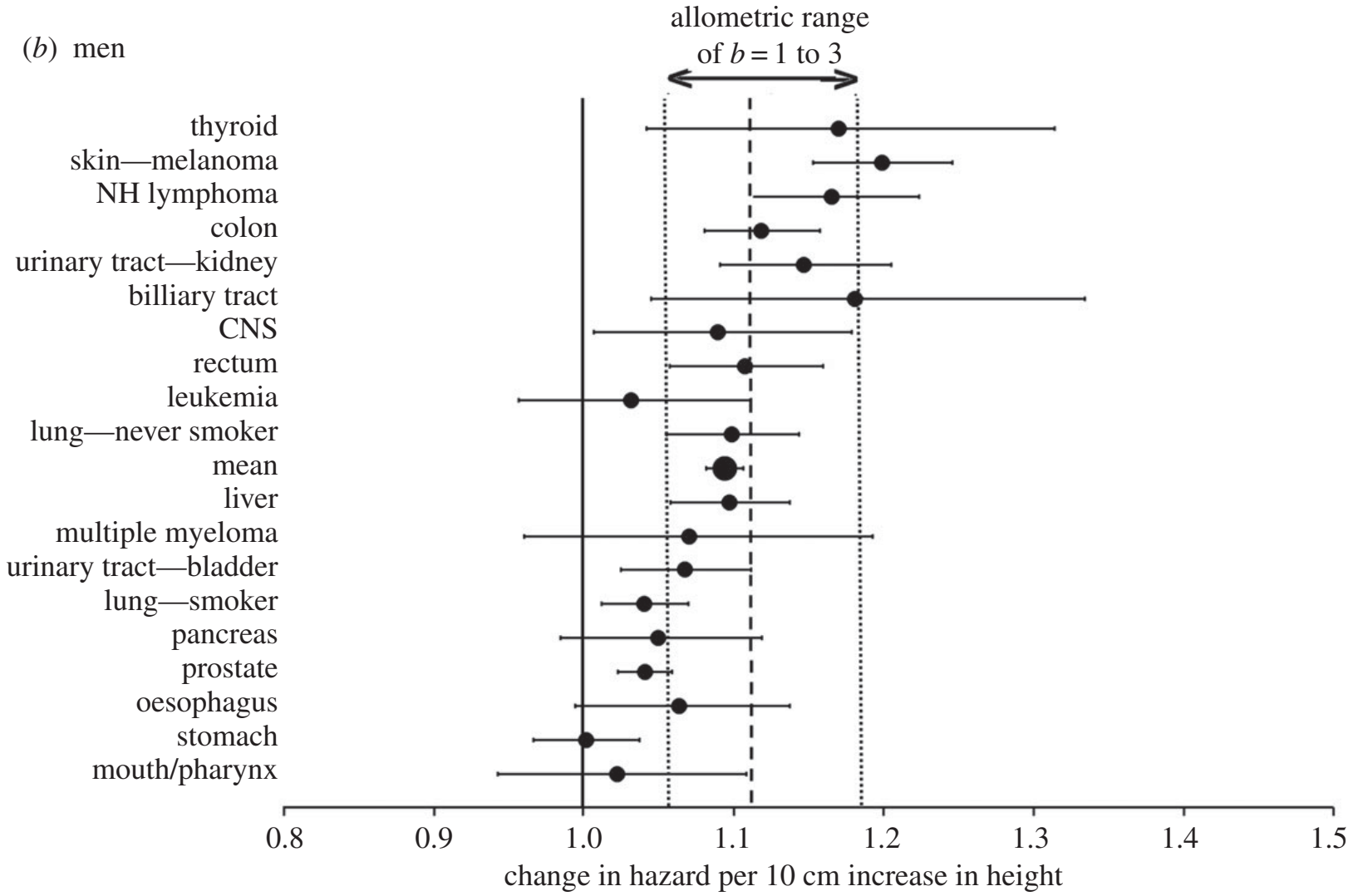


Figure 2. A comparison of the observed and predicted effect of height on the risk of specific cancers: the observed hazard ratio (HR_{10}) and 95% confidence interval linking a 10 cm increase in height to the increased risk of specific cancers, showing only cancers included in at least two of the target studies (for women [22–25]; for men [23–25]). The vertical lines illustrate: no effect of height ($HR_{10} = 1.00$; solid line); the average HR_{10} predicted from the multistage model based on the allometry of human height to overall body mass, which is used as a proxy for cell number (dashed line); and (3) the predicted effect based on the expected extremes of organ cell number allometry to height: linear, $b = 1$ (lower dotted line); and volumetric, $b = 3$ (upper dotted line). For data sources, see electronic supplementary material, table S1.