Supplementary information

There are several considerations that arise with the previously reported derivation of human cell division numbers for tissue-specific stem cells[5]. For one, the analysis conflates mouse with human data which overlooks major differences in their tissues and the numbers of proliferating cells[36-38]. Second, there were extrapolations from the literature that may not hold, such as the assignment of 0.4% as the percentage of esophageal stem cells, a number taken from a peripheral BUdR-labeling experiment in a report whose primary conclusion was that there are no specialized stem cells in the mouse esophagus, but that all of the basal epithelial cells are involved in tissue maintenance and repair[39]. Furthermore, the estimation of neural stems cell divisions was based on an early study that assumed there are no neural cell divisions after birth[40]. However, a more recent study from the same laboratory showed that there is a small but significant amount of neural cell division after birth[41]. Additionally, the authors assumed that the total lifetime stem cell divisions for three developmentally related tissues (pancreas, small intestine, and liver) were identical. This sidesteps many of the current uncertainties concerning the identity of these particular tissue's stem cells. Based on these considerations, it seems unlikely that any truly definitive analysis involving estimations of human tissue stem cell divisions can be made at this time.

Furthermore, there is evidence that a hierarchy of cells, from stem cells to committed progenitor cells to differentiated cells, within the same tissue can serve as the tumor-cell of origin. For example, diethylnitrosamine (DEN) hepatocarcinogenesis appears to involve oncogenic transformation of mature hepatocytes, whereas the carcinogen furan activates bile duct progenitor cells giving rise to cholangiocellular carcinomas, and other carcinogenic regimens leading to liver cancer are thought to target either hepatoblast-like bipolar progenitor cells or the periductual stem cell[42]. Therefore we sought to establish an analytical approach that made as few assumptions as possible about the tumor-cell of origin, yet maintained the intuitive idea that the rate of cell division is an important parameter in the origin of most cancers. We utilized a carefully curated database of numbers at the Database of Useful Biological Numbers (http://bionumbers.hms.harvard.edu) to find estimates of cellular turnover rates for different tissues. The turnover rates for cells in the human prostate gland and breast tissue was taken from the literature[43,44]. These turnover rates (see table below) were used together with the estimates of total tissue cell numbers, and estimated human lifespan of 80 years, to derive an alternative set of numbers used in our analysis in Fig. 3b.

Cancer type	Cancer risk[a]	Homeostatic tissue cell number[b]	Tissue turnover rate (days)[c,43,44]	Lifetime turnover[d]	Lifetime cell divisions[e]
Basal Cell	3.00E-01	1.80E+11	20	1460.0	2.63E+14
Breast	1.23E-01	1.00E+12	85	343.5	3.44E+14
COAD	4.80E-02	3.00E+10	3.5	8342.9	2.50E+14
COAD/FAP	1.00E+00	3.00E+10	3.5	8342.9	2.50E+14
COAD/Lynch	5.00E-01	3.00E+10	3.5	8342.9	2.50E+14
Hepatocellular	7.10E-03	2.41E+11	273	107.0	2.58E+13
Hepatocellular/HCV	7.10E-02	2.41E+11	273	107.0	2.58E+13
Lung adeno nonsmokers	4.50E-03	4.34E+11	8	3650.0	1.58E+15
Lung adeno smokers	8.10E-02	4.34E+11	8	3650.0	1.58E+15
Osteosarcoma	3.50E-04	1.90E+09	90	324.4	6.16E+11
Osteosarcoma arms	4.00E-05	3.00E+08	90	324.4	9.73E+10

Osteosarcoma -head	3.02E-05	3.90E+08	90	324.4	1.27E+11
Osteosarcoma of Leg	2.20E-04	7.20E+08	90	324.4	2.34E+11
Osteosarcoma -pelvis	3.00E-05	2.00E+08	90	324.4	6.49E+10
Prostate	1.40E-01	1.10E+10	500	58.4	6.42E+11
Small intestine	7.00E-04	1.70E+10	3	9733.3	1.65E+14
Testicular germ cell	3.70E-03	2.16E+10	60	486.7	1.05E+13

[a]http://seer.cancer.gov

[b]The numbers are adopted from Table S1 of the supplementary materials in Tomasetti and Vogelstein[5]. For breast and prostate, 0.5 kilogram and 11 grams are used as their average weights, and given that the average weight of a human cell is about 1ng, their homeostatic tissue cell numbers are estimated to be $1x10^{12}$ and $1.1x10^{10}$, respectively.

[c]http://bionumbers.hms.harvard.edu

[d]Lifetime turnover = [80 year * 365 days/year]/Tissue turnover rate (days)

[e]Lifetime Cell Divisions = Homeostatic tissue cell number * Lifetime turnover

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