The Precancerous Niche

Or, why do people with LFS get cancer?

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LFS UK 2022

What is TP53?

The guardian of the genome

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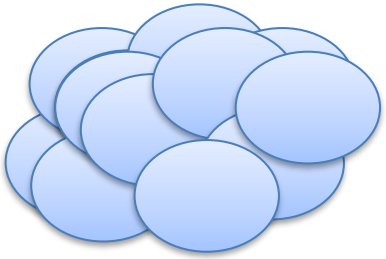
Genetics Home Reference

The *TP53* gene provides instructions for making a protein called tumor protein p53 (or p53). This protein acts as a tumor suppressor, which means that it regulates cell division by keeping cells from growing and dividing too fast or in an uncontrolled way.

The genome is the complete set of genes in your cells – it's the set of DNA instructions for making the proteins (ingredients) that make the cells that make you.

When those instructions pick up mistakes they can lead to uncontrolled cell growth – these cells go rogue and ignore instructions to behave themselves. Cancers are collections of rogue cells.



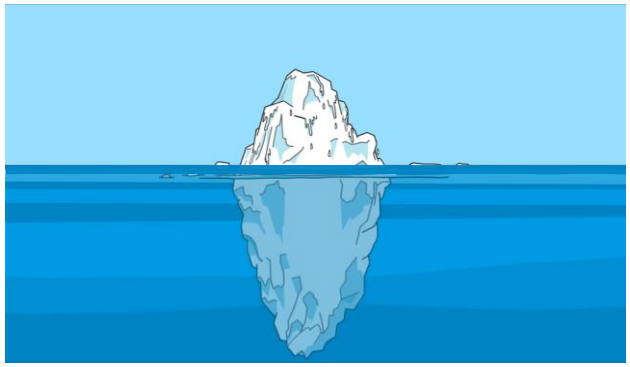
Healthy cells

TP53 gene makes the p53 protein

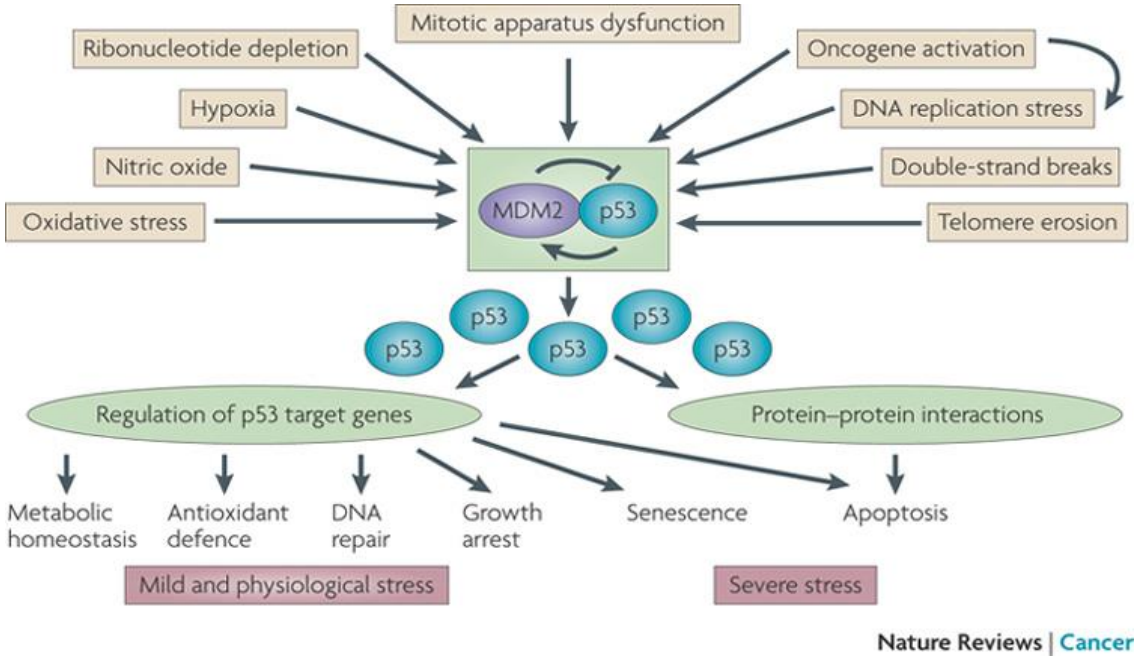
A cell suffers DNA damage….

p53 proteins kick in to get rid of the damaged cell

More than a tumour suppressor



We now know that TP53 is so much more than a tumour suppressor – it handles all kinds of cell stresses… from aging to feeding



Levine AJ and Oren M (2009) **The first 30 years of p53: growing ever more complex**. *Nature Reviews Cancer*, **9**(10), pp. 749–758.

Metabolic Reprogramming

Immune Dysregulation

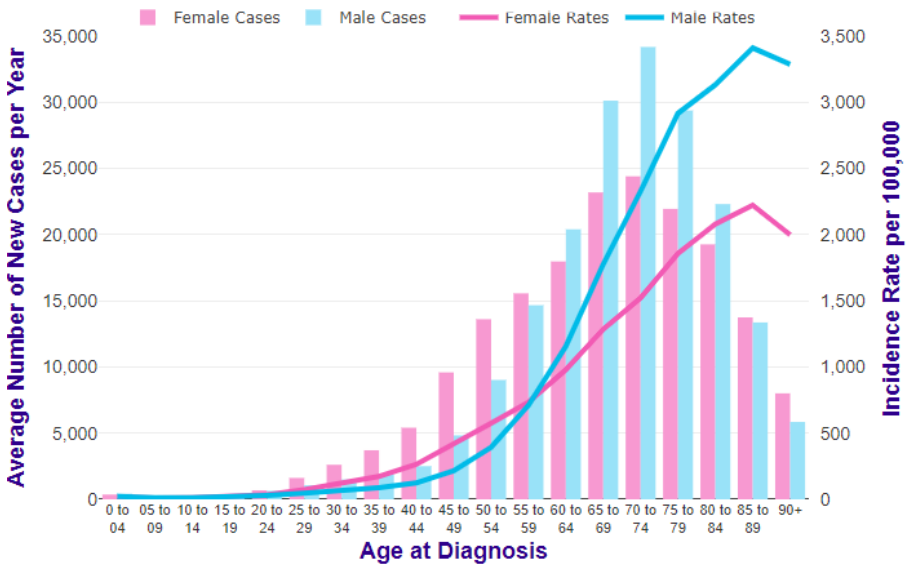
Tissue-specific factors

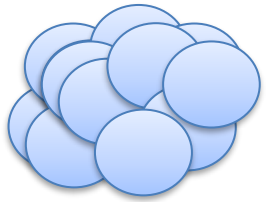
Angiogenesis

Chronic inflammation and oxidative stress

But people with LFS have a 'mutated' TP53 gene – it produces mutated p53 proteins…

How does cancer start?





Healthy cells

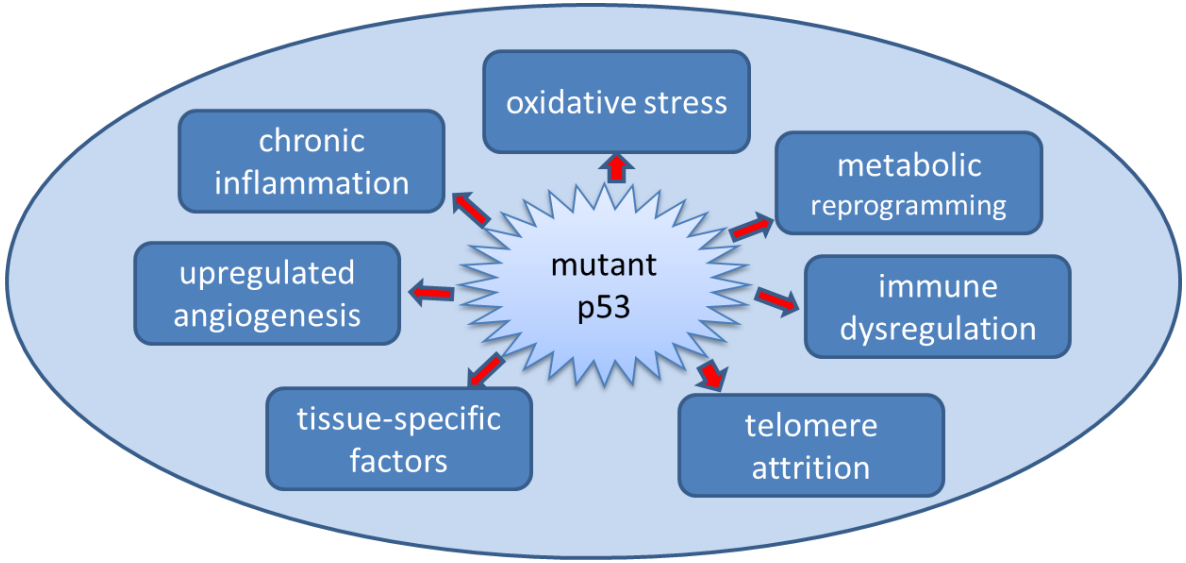
Cells randomly accumulate damage over time – some of that damage is to the DNA that gets passed down to daughter cells

At some point the random accumulation of DNA damage is enough to kick off uncontrolled cell growth that leads to cancer. Often it's the loss of TP53 or other tumour suppressor genes that's the tipping point

DNA damage can come from many sources – smoking, metabolic imbalance, obesity, stress, cosmic rays, some viruses, physical injury, alcohol… The effect of many of these is to cause chronic inflammation/oxidative stress which is what leads to DNA damage

The pre-cancerous niche

People with LFS start with a background of damaged TP53/p53 – but by itself lack of functioning p53 does not cause cancer. However, the non-tumour suppressor functions of TP53 may cause the conditions to *drive* further DNA damage



Is this the picture in people with LFS before they get cancer?

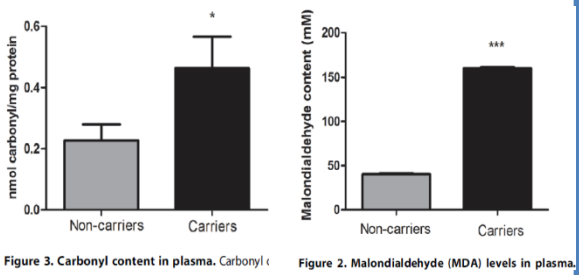


Figure 3. Carbonyl content in plasma. Carbonyl

Figure 2. Malondialdehyde (MDA) levels in plasma.

Data from LFS patients show high basal levels of oxidative stress

Pantziarka P (2015) **Primed for cancer: Li Fraumeni Syndrome and the pre-cancerous niche.** *Ecancermedicalscience*, **9**, p. 541.

Macedo GS et al. (2012) **Increased Oxidative Damage in Carriers of the Germline TP53 p.R337H Mutation**. *PLoS ONE*, **7**(10), p. e47010.

The LFS environment – before cancer

- Metabolic Reprogramming
  - Autophagy
  - Warburg effect
- Immune Dysregulation
  - TLR expression
  - PDL1 expression
- Tissue-specific factors
  - Increased breast aromatase expression
- Angiogenesis
  - VEGF
  - TSP-1
- Chronic inflammation and oxidative stress
  - NFkB
  - PGE2

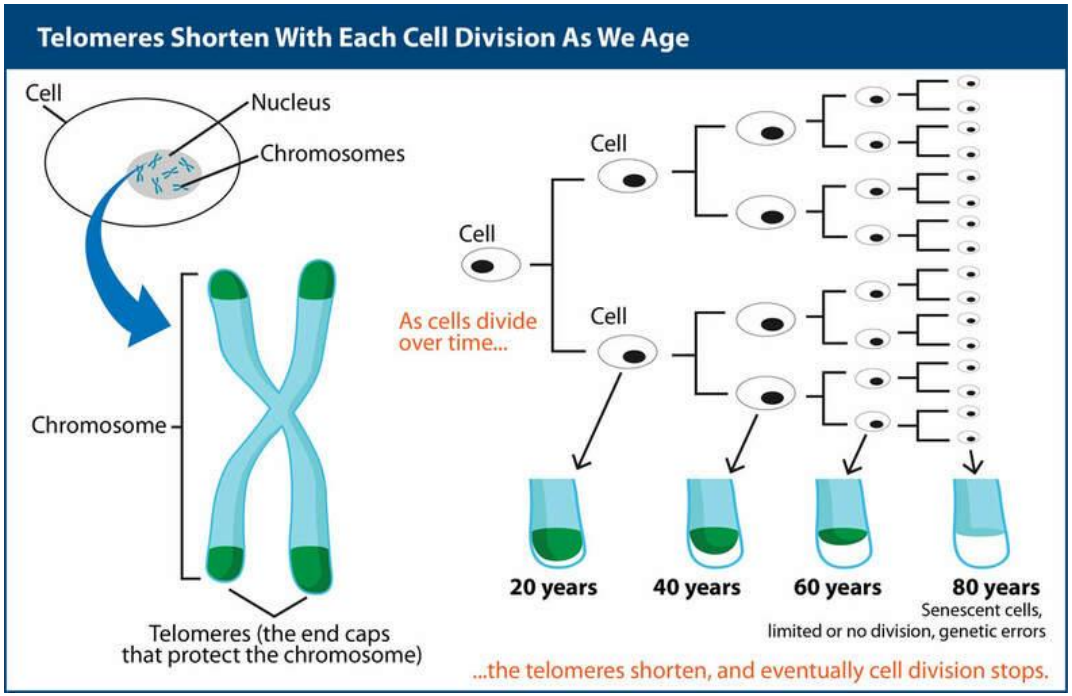
- Increased levels of oxidative stress in people with LFS
- LFS fibroblasts increased levels of VEGF
- LFS fibroblasts have shortened telomeres
- Decreased level of cav-1 (metabolic marker)
- Increased oxidative metabolism
- Increased aromatase expression in breast tissue
- Increased chromosomal instability in LFS fibroblasts

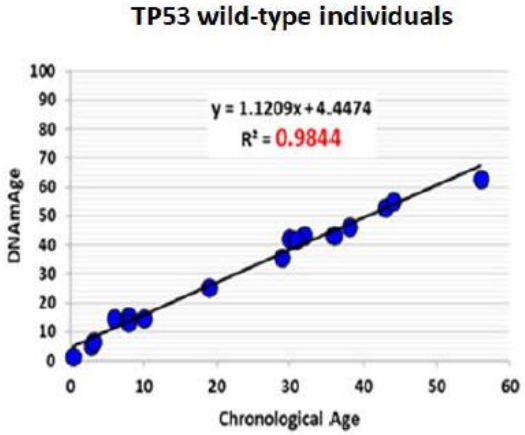
Currently no studies of general health in people with LFS have been carried out. Do they have more or less inflammatory illness, infections, diabetes, rheumatism etc?

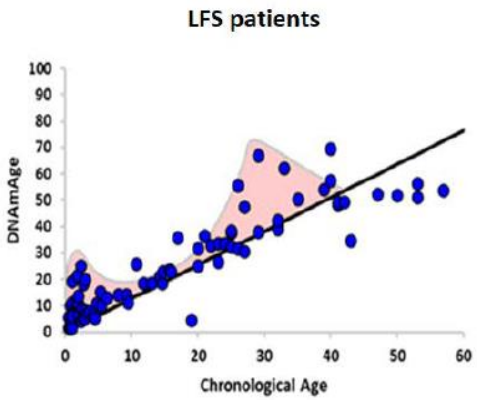
More research is required to understand whether people with LFS have the same range of health conditions as the general population

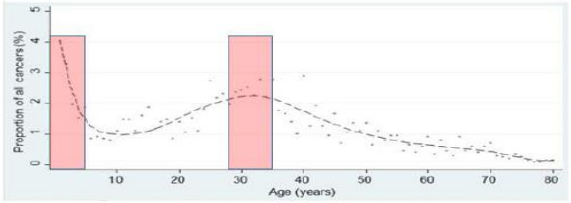
Many of these are also features of aging…

Accelerated aging?









This is strong evidence in line with the precancerous niche hypothesis. So the link with aging and cancer indirectly exists in LFS too…

Abstract # 2114

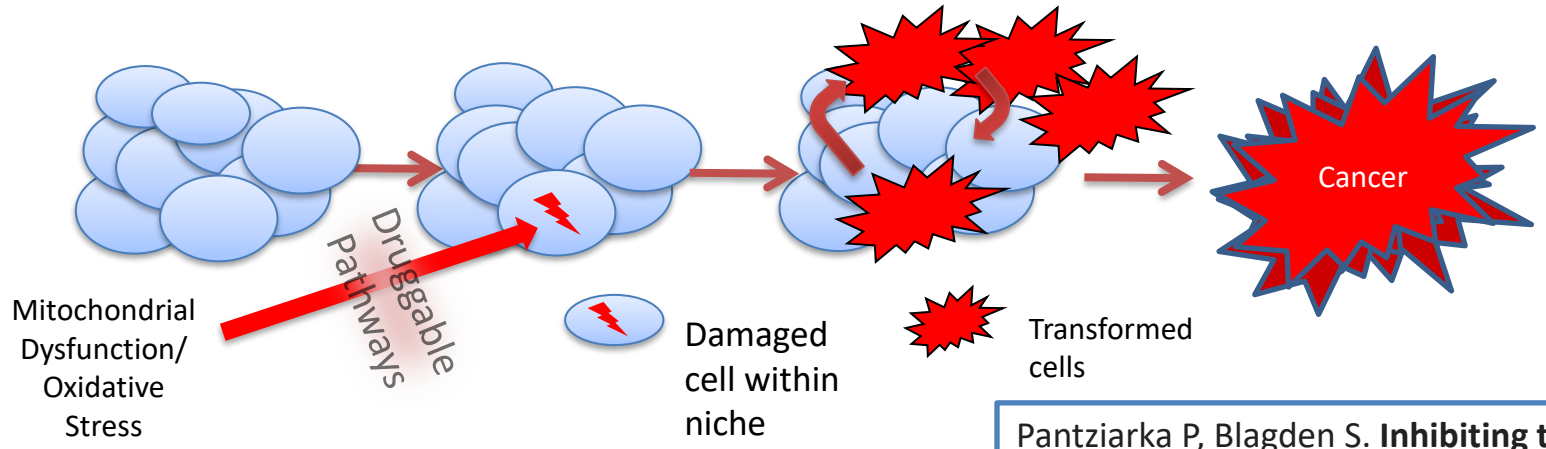
Horvath clock as a predictor of cancer risk in patients with Li-Fraumeni Syndrome

Malgorzata Pienkowska[1], Nardin Samuel[1], Sanaa Choufani[1], Vallijah Subasri[1], Nish Patel[1], Rosanna Weksberg[1], Ran Kafri[1], David Malkin[1]

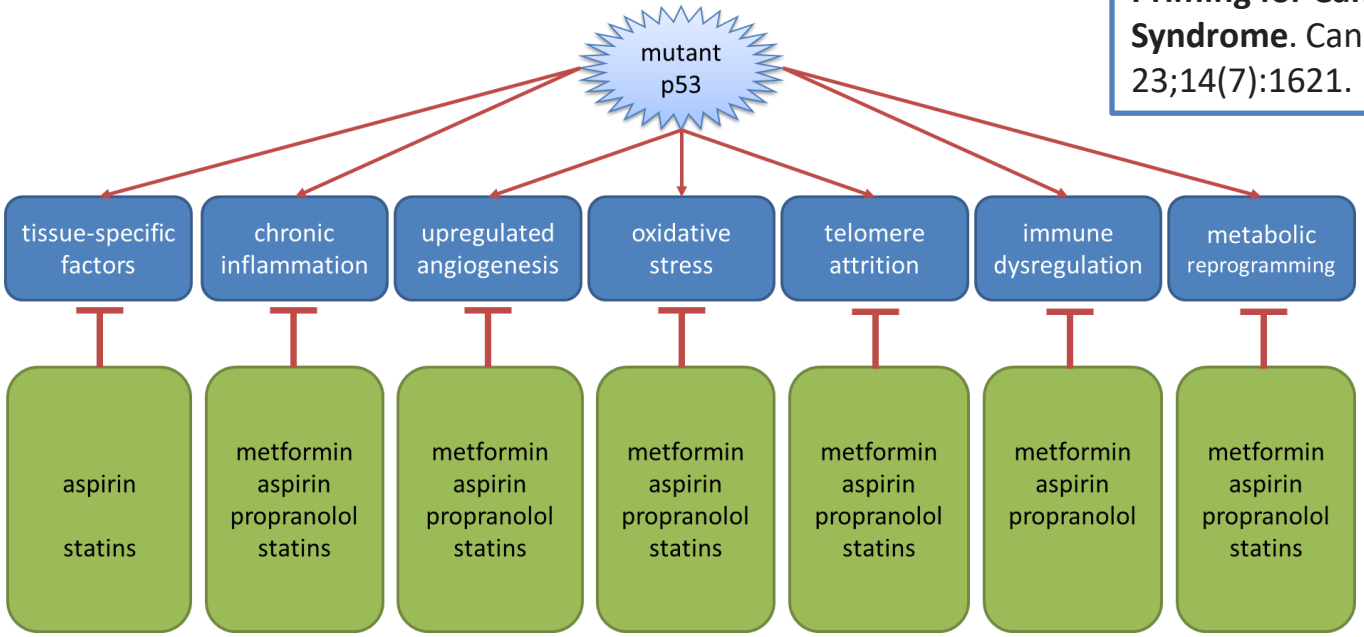
[1]Hospital for Sick Children, Toronto, ON, Canada

SickKids

Inhibiting the Priming for Cancer in LFS



Pantziarka P, Blagden S. **Inhibiting the Priming for Cancer in Li-Fraumeni Syndrome**. Cancers (Basel). 2022 Mar 23;14(7):1621.



The good news – we might be able to block some of the pathways that lead to DNA damage

What does this mean *now*?

- Some diets exacerbate chronic inflammation and oxidative stress
- Obesity increases chronic inflammation and metabolic imbalances
- Excessive alcohol and smoking are no-nos
- Extremes of exercise (too little and too much) can cause inflammation
- Chronic psychological stress has physical effects – including accelerating telomere attrition

But – we don't have the data to definitively pick the best diet, exercise plan or lifestyle choices - yet

Other approaches?

Data from animal models…

Reactivating p53: Data presented at AACR 2017 showed that ReACp53, (an experimental p53 reactivating drug), reduced cancer incidence in a mouse model of LFS (R172H mutation). LFS mice administered the peptide twice weekly showed a 38% improvement in OS.

Soragni A et al (2017) **Targeted tumor prevention in Li-Fraumeni syndrome.** *LB-169 , AACR 2017.*

Rapamycin: p53 KO (+/-) mice administered rapamycin (an mTOR inhibitor) showed reduced tumour incidence and increased overall survival (by 28% in young mice, 10% in older).

Komarova E et al. (2012) **Rapamycin extends lifespan and delays tumorigenesis in heterozygous p53+/- mice.** *Aging*, **4**(10), pp. 709–14.

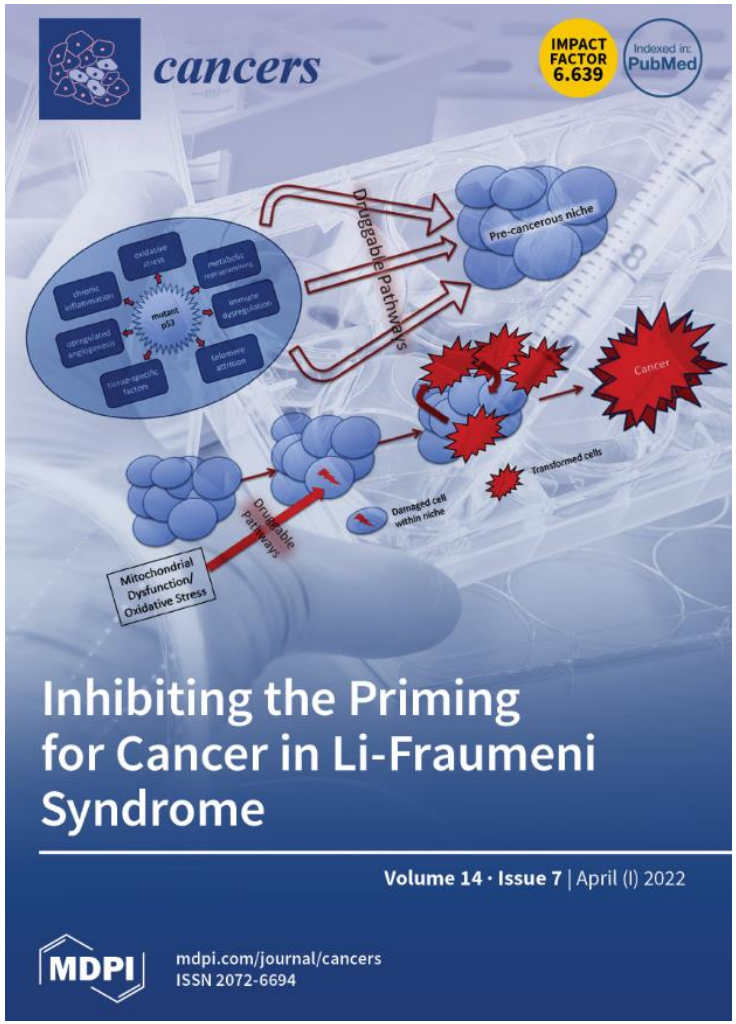
Diet: p53 KO (+/-) adult mice on calorie restricted (60% of calories compared to normal diet) or 1 day/week fasting showed increased overall longevity compared to unrestricted diet. CR or fasting mice had reduced body weight and reduced IGF1 and leptin levels.

Berrigan D et al (2002) **Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice.** *Carcinogenesis*, 23(5), pp. 817–22.

We need to learn more…

- Can we detect the changes in LFS cells before they become cancers?
- Can we see the pre-cancerous niche using imaging (MRI)?
- Can we correlate inflammation rates with cancer incidence in LFS?
- Can we work out which diet and lifestyle changes reduce cancer incidence?
- Which drugs reduce cancer risk in LFS – and why?

Questions?



Editorial › Cancer Epidemiol Biomarkers Prev. 2022 Sep 2;31(9):1673-1674.
doi: 10.1158/1055-9965.EPI-22-0609.

Walk More, Eat Less, Don't Stress

Omer Kucuk [1]

Affiliations + expand

PMID: 36052489 DOI: 10.1158/1055-9965.EPI-22-0609