Review Article

Is There a Hereditary Cancer Resistance Genotype?

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Most of the knowledge about germline related cancer risks emerged from pioneering studies of families with increased cancer incidence. This led to the discovery of the chapter of hereditary cancer predisposing syndromes. More than 50 syndromes have been identified and thoroughly studied. While most germline studies focused on pathogenic variants that increase cancer risk (e.g. BRCA1/2, CHEK2 with ORs up to 8.6), little research has been dedicated to the opposite situation, that is germline mutations or variants that decrease the risk of cancer. The methods employed in these cancer risk reduction studies were not centered on family history of cancer but rather on genome wide association studies (GWAS). A body of knowledge has been accumulating in this regard slowly but steadily. The aim of this review is to summarize the main genetic features that can reduce the risk of develop cancer in general and in some specific cancers as well.

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Introduction

Without entering into statistical details, we can roughly say that one third of humans develop a cancer during their lifetime. Approximately 10% of all cancers are related to hereditary cancer predisposing syndromes. In these cases, cancer predisposition (but not cancer) “was in the genes” even before birth.

However, two thirds of the population will never develop a cancer. Many in this “no-cancer” population never develop a cancer because they die from accidents or other diseases before reaching the age of high cancer incidence. Others, who live long enough to reach the high “risk age” do not develop a cancer.

We know a lot about the people who develop cancer at some point in their lives. We also have a fairly good knowledge about those who are born with a hereditary cancer predisposition syndrome. What do we

know about those who never develop a cancer? Almost nothing.

What do we know about those families where cancer is never present? The answer is again the same: almost nothing.

Not all people that “live dangerously” such as smoking two packs of cigarettes a day, do not develop a cancer. Many will and many will not have a cancer. Therefore, we must ask: is cancer development a random process? The answer is that in many cases it is random, in many more there are predisposing environmental causes, in some cases there is a genetic predisposition, but undoubtedly there is a small group of people that are more resistant to cancer.

How do we know this?

Firstly, there is animal evidence in this regard (see below). Secondly, the three-pack-a-day-for-50-years smoker that ends his days thanks to emphysema but not cancer is a hint towards some resistance to cancer in these few individuals.And thirdly, place some interesting laboratory evidence has been collected in the last ten years, clearly showing that there is a cancer resistant phenotype based on specific hereditary genetic variations.

Hereditary cancer predisposition syndromes have been thoroughly investigated in the last thirty years. A lot is known about them but there are still many gaps to fill. On the other hand, very little is known about what we have called here “hereditary cancer resistance”. In fact, it is so little that we can even doubt its existence.

Actually, there is no known “hereditary cancer resistance” in humans in the sense of families passing down genes that make them broadly immune to cancer. But there are some very interesting biological mechanisms and rare genetic traits that can make some people less susceptible to certain cancers.

Interestingly, there is quite a bit of evidence regarding a cancer resistance phenotype in animals.

Animal evidence

► **Elephants** are the paradigm of a hereditary cancer resistance-like profile[1][2][3]. Abegglen et al. [4] suggested that elephants are cancer resistant by virtue of multiple copies of gene *TP53* and enhanced responses to DNA damage. Elephants have been also used as the best example of the Peto paradox. This paradox highlights the observation that cancer risk does not appear to scale with size in the animal kingdom. The underlying premise is that more cell division (to make and sustain a larger animal) along with longer life span might be expected to carry a proportionally greater mutational and malignancy

risk[5][6]. In elephants this does not happen. Interestingly, elephants have 20 copies (40 alleles) of the p53 gene while humans have only one (two alleles, one in each allele). Therefore, elephant cells are hypersensitive to DNA damage. Furthermore, instead of trying to repair a heavily damaged cell, which might later turn malignant, elephant cells are quick to destroy these cells. The elephant mechanism of strict DNA integrity surveillance and rapid apoptosis is the product of genetic redundancy.

► **Naked moles** also seem to have cancer resistance features but they seem to be a consequence of mechanisms different from those found in elephants[7][8][9]. In the case of the naked mole, cancer resistance seems to be associated with a particular extracellular matrix chemistry that leads to early contact inhibition. Contact inhibition is a mechanism discovered in cell cultures in which cells stop replicating when they establish contacts with other cells. The naked mole has a very thick ECM formed by high molecular mass hyaluronan. This hyaluronan acts as a chemical cage that prevents cells from further replication through contact inhibition.

► **Bowhead whales** have enhanced DNA repair pathways. These whales have built up a very efficient DNA repair mechanism that, like elephants, have duplicated tumor suppressor genes. They can fix double-strand breaks in DNA, the most dangerous type of damage, much faster and more accurately than humans.

► **Mus spretus**, a widely used mouse for experimental genetics, comparative genomics, and particularly in identifying genetic variations and adaptive traits, shows innate resistance to tumors in the skin, lung, liver, and other sites due to multiple dominant genes acting at tissue organization levels.[10]. The mechanism in this case is a very efficient immune system using interferon-mediated cell death mechanisms.

►**Some long-lived animals** have a slower accumulation of mutations due to a lower rate of mutations.

► **Microbats,** specifically species like the Little Brown Bat (*Myotis lucifugus*) and the Mesoamerican Mustached Bat (*Pteronotus mesoamericanus*), are some of nature's most successful cancer survivors. Despite having small bodies and high metabolic rates (factors that usually lead to high mutation rates), they live 20-40 years with almost no recorded cases of cancer.

Recent research has found that microbats use a "high-maintenance" biological strategy that differs significantly from large animals like elephants. Mechanisms involved in the anti-cancer traits of microbats include[11][12][13]:

1. A high activity p53 system. The p53 system is highly active although there are no extra copies as in elephants (with the exception of *M. lucifugus* that has a TP53 duplication).
2. Reduced growth hormone signaling.
3. Compared to human genomes, microbat genomes have a massive "enrichment" of anticancer genes.
4. Bat fibroblasts exhibit increased TP53 and MDM2 transcripts and elevated p53-dependent apoptosis.
5. A high-performance immune system: Bats are known for hosting viruses without falling ill, and their immune systems are also unusually good at identifying and eliminating cancer cells. While human immune systems tend to weaken and grow more inflammatory with age, bats maintain balance, keeping both infections and age-related diseases like cancer in check.
6. Bats maintain the enzyme telomerase, for humans usually only found in stem, reproductive, and cancer cells, allowing their cells to keep dividing without degrading DNA, a feature that supports tissue repair. In most animals, this would raise the risk of cancer. But bats' high *p53* activity steps in as a safeguard, removing any cells that start to go rogue.

The above examples show that the animal kingdom has many examples of hereditary cancer resistance traits. Unfortunately, humans lack these extreme adaptations. However, this is not completely true. Some individuals show some genomic predisposition for preventing cancer. There is now evidence that some people inherit genes that reduce cancer risk. These aren't "superpowers," but variations in DNA repair genes, immune-system genes, or tumor-suppressor pathways that can make cancer less likely to develop.

Examples include:

- Variants that improve DNA repair efficiency
- Variants that enhance immune surveillance
- Variants that reduce inflammation (chronic inflammation increases cancer risk)

As a striking difference with hereditary cancer predisposition syndromes the traits of hereditary cancer resistance are subtle and do not confer absolute protection. Here the elephants come to our help again: there are elephants with cancer, however, the risk of developing a cancer is lower. This means that elephants can develop cancer, but they do so at remarkably low rates compared to humans and other animals of similar size and lifespan. Given that elephants have about 100 times more cells than humans and live for many decades, they should theoretically have a much higher cancer risk. Yet, they don't.

Research has uncovered several biological mechanisms that help explain elephants' cancer resistance such as:

- **Multiple Copies of TP53**: Elephants have at least 20 copies of the TP53 gene, a crucial tumor suppressor, while humans have only one. TP53 plays a key role in detecting DNA damage and initiating cell death (apoptosis) in potentially cancerous cells.
- **Enhanced Apoptosis**: Elephant cells are more likely to undergo programmed cell death when DNA damage is detected preventing the propagation of mutations.
- **Other Tumor Suppressor Genes**: Studies suggest that elephants may also have evolved additional tumor-suppressing mechanisms beyond TP53, contributing to their resilience[14][15][16][17].

Despite their robust defenses, elephants are not completely immune to cancer. Some cases have been documented, particularly in captive elephants, but the overall incidence remains significantly lower than in humans[18].

At this point, we can say that there are genetic germline variants that can reduce cancer risk, although mechanisms and inheritance are far from clear. Humans do not have strong, well-defined hereditary cancer resistance mechanisms. Humans can inherit traits that modestly reduce cancer risk.

Considering that hereditary cancer resistance is almost a "rare" topic in cancer some basic definitions are necessary.

Hereditary resistance to cancer refers to inherited genetic variants that protect individuals from developing certain cancers, countering the more commonly studied hereditary risks that increase susceptibility.

While humans do not have 20 copies of p53, we can lower susceptibility by managing the "external" triggers of mutations. According to current research, nearly 40% of human cancers are preventable through lifestyle.

Unfortunately, based on the current scientific literature, there is no direct evidence describing groundbreaking specific germline mutations that confer resistance to the development of cancer in humans.

Human gene germline variations probably related to hereditary cancer resistance

Certain germline mutations in humans can reduce cancer risk by altering gene expression or immune responses, countering the more commonly known risk-increasing variants. Recent research highlights specific protective examples, particularly against blood cancers.

Certain human leukocyte antigen (HLA) alleles, especially Class I types like those in supertypes A03, A24, B27, B44, and B52, show protective effects against various cancers by influencing immune recognition of tumors[19]. Overall, HLA alleles exhibit a preponderance of protective over susceptibility associations across 30 cancer types. About 78% of 127 tested alleles have mixed effects, but Class I genes A and B lean protective.

SNPs (single nucleotide polymorphisms) in genes like hOGG1 (rs1052133) and FEN1 (rs174538, rs4246215) offer protection against Wilms tumor via enhanced DNA repair[20]. Certain p53 mutations, such as R273H, may sensitize tumors to immunotherapy despite loss of suppressor function[21]. p53 mutation R273H was found to cause excessive DNA replication, leading to aggressive cell proliferation promoting cancer growth. However, paradoxically, at the same time, excessive DNA proliferation triggered a strong immune response toward the cancer cells. This response was driven by activation of the cGAS-STING pathway, a key part of the body's innate immune response.

Certain germline mutations beyond MSI2 and HLA variants offer protection against specific cancers by enhancing DNA repair, modulating immune responses, or inhibiting tumor growth pathways. Germline variants in immune-related genes like IFIH1 and TMEM173 (STING1) modulate interferon signaling, potentially aiding anti-tumor immunity[22].

Rare germline loss-of-function mutations in the AURKB (Aurora Kinase-B) gene, which encodes Aurora kinase B involved in mitosis and cytokinesis, have been associated with protection against across multiple types of cancer. A large-scale genomic study by deCODE genetics analyzed over 130,000 cancer patients and 733,000 controls, identifying these variants as conferring a reduced overall cancer risk with an odds ratio of 0.84[23].The study used gene-based burden tests on rare germline variants from European descent cohorts. Loss-of-function in AURKB protected against any cancer irrespective of site, marking it as one of the first identified protective genes alongside PPP1R15A for breast cancer. AURKB typically acts as an oncogene when overexpressed, promoting tumor proliferation, cell cycle progression,

and poor prognosis in cancers like renal clear cell carcinoma, and lung adenocarcinoma. However, germline inactivation disrupts essential mitotic processes, potentially preventing oncogenic transformation without fully compromising viability in carriers. This contrasts with somatic AURKB inhibition strategies explored for cancer therapy[24][25][26]. No individual cancer types showed stronger associations beyond the overall effect, highlighting AURKB's role in universal mitotic fidelity essential for preventing oncogenesis. This suggests therapeutic inhibition of AURKB as a potential strategy, though germline carriers remain viable. Germline loss-of-function variants in AURKB are rare across populations, with no evidence of commonality in any specific ethnic or geographic group.

1) Leukemia

Agarwal et al.[27] have recently identified an inheritable genetic variant that reduces the risk of leukemia. Healthy aging tissues often harbor a substantial burden of cancer driver mutations. As people age, they often develop clonal hematopoiesis, or accumulation of blood cells with specific mutations that offer a survival advantage to those cells but not to the entire organism. Fortunately, not all patients with clonal hematopoiesis develop clinical manifestations, and only rarely does clonal hematopoiesis develop cancer, but it does increase the long-term risk of some blood cancers. By analyzing data from tens of thousands of patients and hundreds of thousands of controls across multiple studies, Agarwal *et al*. identified and studied the mechanism of a genetic variant that has the opposite effect, slowing down the expansion of clonal hematopoiesis and decreasing the risk of malignancy.

Agarwal et al. also identified “a non-coding regulatory variant, rs17834140-T, that significantly protects against clonal hematopoiesis and myeloid malignancies by down-regulating hematopoietic stem cell-selective expression and function of the RNA-binding protein MSI2 (also known as Musashi-2).” They also identified that populations with this variant had a higher level of a RNA network that modifies the post-translational expression of the MS12 gene.

This finding deserves a deeper analysis of the MS12 gene. MSI2 normally promotes stem-cell self-renewal. MSI2 is an RNA-binding protein that regulates stem-cell fate, asymmetric cell division, and translation of key mRNAs involved in growth and survival.

In many cancers, MSI2 is overactive, driving increased proliferation, blocked differentiation and enhanced survival of pre-leukemic cells. This makes MSI2 a known oncogenic driver in leukemia.

The protective variant reduces MSI2’s oncogenic activity. The MSK study found that the protective variant:

- alters a regulatory region of the MSI2 gene
- reduces MSI2 expression in hematopoietic stem cells
- lowers the ability of mutated clones to expand

This is crucial because clonal hematopoiesis is a major precursor to blood cancers.

(The MSK study refers to MSK-IMPACT, a large-scale tumor sequencing initiative by Memorial Sloan Kettering Cancer Center (MSK) to identify actionable mutations in cancer).

In simple terms:

Less MSI2 → fewer opportunities for mutated blood-cell clones to take over → lower cancer risk.

Reduced MSI2 disrupts cancer-promoting pathways

MSI2 controls translation of many mRNAs. When MSI2 levels drop, several cancer-relevant pathways weaken:

Reduced translation of growth-promoting mRNAs

MSI2 normally represses or activates specific targets that regulate:

- cell cycle progression
- survival signaling
- stem-cell renewal

Lower MSI2 means these pathways are less active.

Lower activation of downstream regulators like EIF3A

EIF3A is a key MSI2 downstream effector involved in translation initiation.

Reduced MSI2 → reduced EIF3A activity → reduced protein synthesis needed for malignant growth.

Less support for pre-leukemic stem cells

MSI2 is essential for leukemia stemcell maintenance.

The protective variant weakens this support. The protective variant specifically blocks expansion of mutated clones. The protective variant does not prevent mutations, it prevents mutated cells from gaining dominance.

In summary: The MSI2 protective variant reduces MSI2 expression, weakening stemcell self-renewal and translation pathways that mutated blood-cell clones rely on, thereby lowering the risk of blood cancers.

How many people have the protective variant of MSI2?

We do not know. What we do know is that it is a rare variant of the gene.

2) Bladder and ovarian cancer

Germline Pathogenic Variants (gPVs) in Cancer-Predisposition Genes A pan-cancer analysis found that cancers with a greater proportion of gPVs generally exhibited improved survival[28]. In bladder and ovarian cancer, gPV-positive patients showed significantly improved survival, which was associated with up-regulation of immune-stimulatory transcriptomic pathways (Shen, 2025). Most of these beneficial gPVs were in the homologous recombination deficient (HRD) variant category, suggesting they might create a pro-inflammatory immune response that aids survival (Shen, 2025).

3) Lung cancer

Certain rare genetic variants appear to confer *protection* against lung cancer, often by enhancing DNA repair, detoxification of carcinogens, or immune surveillance. These protective mutations are less common and less studied than risk variants, but current research is shedding light on them.

Germline Variants in Small Cell Lung Cancer (SCLC) Patients with SCLC carrying pathogenic germline variants in cancer-predisposing genes such as *RAD51D*, *CHEK1*, *BRCA2*, and *MUTYH* demonstrated longer recurrence-free survival after platinum-based chemotherapy[29]. These findings suggest that an inherited predisposition in SCLC, characterized by specific germline mutations, can lead to a more favorable response to certain treatments, thereby enhancing survival. For instance, a patient with a germline pathogenic mutation of *BRIP1* (a homologous recombination-related gene) showed a notable disease response to agents synthetically lethal with homologous recombination deficiency).

CHRNA5/A3/B4 locus (15q25.1): This nicotinic acetylcholine receptor cluster influences smoking behavior. Protective alleles reduce nicotine dependence, leading to lower cumulative exposure to tobacco carcinogens. Many protective variants show ethnic variation. For example, CHRNA5 rs16969968 is more common in European populations. Protective effects often depend on environmental exposures (e.g. smoking, radiation, air pollution). However, No single variant offers complete protection. Instead, a combination of low-risk alleles and favorable lifestyle factors contributes to reduced susceptibility[30].

DNA repair efficiency: Variants in XRCC1 (e.g. Arg399Gln) and ERCC1 may enhance repair of bulky adducts and oxidative damage, especially relevant in smokers.

In never-smokers, certain genetic variants appear to confer protection against lung cancer by enhancing DNA repair, immune surveillance, or reducing susceptibility to environmental carcinogens like air

pollution. These variants are distinct from those in smokers and often involve different biological pathways.

Certain HLA haplotypes are more efficient at presenting tumor neoantigens, improving immune clearance in never-smokers[31].

TP63 (3q28 locus) variants have been associated with reduced lung cancer risk in East Asian never-smokers, possibly via epithelial homeostasis[32].

Telomere maintenance.- Protective alleles may preserve telomere length and genomic stability reducing transformation risk[33].

Genome wide association studies identified GPC5 gene variants as protective in never-smokers by inhibiting cell proliferation in lung tissue.

4) Breast cancer

HLA alleles like DQB*03032 and DRB*111 associate with lower early-onset breast cancer incidence, possibly via enhanced immune presentation of tumor antigens[34].

The genetic polymorphism *LEPR K109R* (rs1137100) may decrease susceptibility to breast cancer, particularly under the additive genetic model. This variant has also been associated with a reduced risk of lung cancer under heterozygous co-dominant, recessive genetic, and additive genetic models[35].

It was suggested that certain BRCA1 variants could have a protective effect against cancer. However this does not seem true. For a BRCA1 coding variant to be called truly protective, it would need to reduce cancer incidence below that of people with two wild-type alleles; at present, such an effect has not been convincingly demonstrated in large human datasets. Claims that certain BRCA1 changes are “protective” usually reflect either: (a) benign polymorphisms misinterpreted in small studies, or (b) context-specific effects (e.g. better prognosis or response to therapy) rather than reduced incidence of primary cancer.

In clinical genetics, BRCA1 variants are essentially dichotomized into pathogenic/likely pathogenic (risk-increasing) versus benign/likely benign (neutral), with the latter managed as general-population risk rather than as “protected.”

However, certain hypomorphic (partial function) BRCA1 variants and genetic modifiers in BRCA1 mutation carriers confer lower-than-average risks relative to classic pathogenic variants. These are relevant in hereditary cancer counseling rather than primary prevention[36].

Rare predicted loss-of-function variants in PPP1R15A correlate with lower breast cancer incidence in large genomic studies, suggesting that reduced gene activity impedes early tumor development[37].A large-scale genomic study identified that carriers of these rare PPP1R15A loss variants have 53% lower odds of developing breast cancer (odds ratio [OR] = 0.47). This protective effect stems from heterozygous loss, highlighting PPP1R15A as one of the first genes where reduced activity prevents tumorigenesis.

This finding also suggests that inhibition of PPP1R15A may be a preventive strategy for breast cancer. As of early 2026, no clinical trials specifically test PPP1R15A inhibition for breast cancer prevention; research focuses more on its role in stress responses and immunotherapy enhancement[38].Pharmacological agents like Sephin1 inhibit PPP1R15A and show antitumor effects in models of liver fibrosis-associated cancer by reducing immunosuppressive myeloid-derived suppressor cells.

5) Cervical cancer

Allele HLA-DQB1 rs55986091 A offers protection against cervical cancer, likely through better viral antigen handling[39].

Two genetic variants within microRNA-binding sites of *RAD51B*, the G allele of rs963917 and the C allele of rs963918, have been associated with a **decreased risk of cervical cancer** in Chinese women. The haplotype GC (from these two variants) also correlated with a lower risk[40].

6) Prostate cancer

Certain genetic variants, particularly single nucleotide polymorphisms (SNPs), have been associated with reduced prostate cancer risk. Genome-wide association studies (GWAS) have identified over 100 SNPs with modest effects on prostate cancer risk, where certain alleles decrease incidence. Cumulative effects from multiple protective SNPs can further lower risk, especially in combination[41].

► Genetic variants near *CYP24A1*, specifically allele rs6013897 associated with lower serum 25-hydroxyvitamin D levels, have been linked to a **decreased risk of aggressive prostate cancer**[42], A polygenic score combining four single nucleotide polymorphisms (SNPs) related to lower vitamin D alleles also showed a significantly reduced risk for aggressive prostate cancer

► The non-synonymous *KLK3* SNP, rs17632542 (leading to an Ile163Thr-substitution in PSA), is associated with **reduced prostate cancer risk** and smaller subcutaneous tumors due to its impact on PSA

proteolytic activity[43]. However, this variant also exhibits a dual effect, being linked to higher metastatic potential and an increased risk for aggressive disease and prostate cancer-specific mortality.

► Genotypes GA/GG in *TPCN2* rs3750965 have been associated with a significantly **lower risk of developing prostate cancer**[44].

► The *P2RX4* rs25644 allele GG has been associated with a **low risk of cancer recurrence** in patients with prostate cancer[44].

► Heterozygotes for the minor allele of rs2302427 in EZH2 show significantly reduced prostate cancer risk (OR 0.63)[45].

► The VEGF -1154 A allele has been linked to lower prostate cancer risk in some studies[45].

► The minor allele of rs1567669 at NKX3-1 also confers protection among heterozygotes (OR 0.71)[45].

7) Oral cancer

The *MET* rs1621 polymorphic variant "G" has been significantly associated with a **lower risk of oral cancer**, particularly among cigarette smokers. The genotypic variant "G" of *MET* rs33917957 has been associated with a **lower risk of cell differentiated grade** in male oral cancer patients[46].

8) Endometrial cancer

Several genetic variants that may *reduce* the risk of endometrial cancer have been identified:, often by modulating hormone metabolism, immune surveillance, or DNA repair. These protective alleles are typically low-penetrance and population-specific, but they offer insights into cancer resistance mechanisms.

Mendelian randomization analyses suggest that genetically increased levels of low-density lipoprotein (LDL) cholesterol are associated with **lower risks of endometrial cancer** across all histologies, including endometrioid and non-endometrioid subtypes. This association for non-endometrioid endometrial cancer remained significant even after adjusting for body mass index[47].

KLF5 in 13q22.1 is a gene with tumor suppressor activity. Variations of this gene that increase its expression have been found[48]. KLF5 gene encodes the Krueppel-like factor-5 protein which acts as a transcription factor. High KLF5 expression has been found to be associated with higher survival in lung cancer patients

9) Colorectal cancer

The *CYP1A1* rs4646903 CC homozygous variant showed a **reduced risk of rectal cancer** (Cho, 2017). The protective effect of dietary flavonol intake on colorectal cancer risk was stronger in carriers of this CC homozygous variant[49](Cho, 2017). Genotypes GA/GG in *P2RX4* rs28360472 were associated with a **decreased risk of colon cancer.**

COLCA1, COLCA2, and POU2AF2 located on chromosome 11q23.1 gene variants have been shown to enhance immune surveillance and epithelial barrier function. Variant rs3087967 in this locus are associated with *reduced* CRC risk, possibly by modulating immune cell infiltration and mucosal integrity[50].

Lead SNPs at 11q23.1 (e.g., rs3802842) are associated with *modulation* of CRC risk. While some alleles increase risk, others appear protective. The locus regulates **POU2AF2**, a transcriptional coactivator expressed in **colonic tuft cells**, which are rare chemosensory epithelial cells involved in immune signaling. **Protective alleles** are associated with *higher expression* of POU2AF2 and **COLCA1/COLCA2**, enhancing mucosal immunity and epithelial integrity.

Tuft cells act as immune sentinels, producing IL-25 and interacting with type 2 innate lymphoid cells (ILC2s). Variants that increase **POU2AF2** expression promote tuft cell differentiation and function, potentially enhancing **immune surveillance** and reducing tumor initiation. Therefore, individuals with protective variants may have a **more robust epithelial-immune interface**, reducing susceptibility to inflammation-driven tumorigenesis.

Low penetrance SNPs in genes SMAD7 and TGFBR2 modulate TGF-β signaling and inflammation and some alleles are associated with lower colorectal cancer risk probably by maintaining epithelial homeostasis[51]. **SMAD7** is an intracellular inhibitor of **TGF-β signaling**, a pathway with dual roles in CRC: tumor suppression in early stages, but pro-tumorigenic in late stages. The **rs4939827 (T>C)** polymorphism is associated with *reduced CRC risk* in multiple populations[52][53].

Lower SMAD7 expression (linked to the protective allele) allows more active TGF-β signaling, which suppresses epithelial proliferation and inflammation.

Furthermore, SMAD7 prevents immunogenic cell death in colorectal cancer[54].

10) Pancreatic cancer

Although most germline mutations (e.g. in *BRCA1/2*, *PALB2*, *ATM*) increase pancreatic cancer risk, some variants may offer relative protection[55]:

SPINK1 N34S variant: While Serine Peptidase Inhibitor Kazal Type 1 (SPINK1) N34S variant is associated with acute and chronic pancreatitis[56][57], some studies suggest it may not significantly increase pancreatic cancer risk, and in certain populations, it may even be neutral or protective depending on co-inherited alleles[58][59]. SPINK1 encodes a protein with pancreatic secretory trypsin inhibitor abilities.

ABO blood group O: Individuals with blood group O have a lower risk of pancreatic cancer compared to non-O groups (A, B, AB), possibly due to altered glycosylation patterns affecting tumor cell adhesion and immune recognition.

HLA-DQB1*06:02 allele: Associated with enhanced immune surveillance and reduced pancreatic cancer risk in some cohorts.

Variants in IL-10 and TGF-β1: Certain polymorphisms in these cytokine genes may modulate the tumor microenvironment toward an anti-tumor phenotype, though findings are population-specific and not yet clinically actionable.

Mitochondrial DNA variants: Some mtDNA haplogroups may influence oxidative stress and apoptosis sensitivity, potentially affecting tumor initiation.

Epigenetic regulators: Variants in genes like *KDM6A* and *ARID1A* may modulate chromatin accessibility in ways that suppress tumorigenesis in specific contexts.

11) Glioblastoma (GBM)

While glioblastoma is driven by aggressive oncogenic mutations, a few rare genetic variants, particularly in IDH1/2, MGMT, and HLA loci, have been associated with improved prognosis, therapy response, or reduced tumor aggressiveness. These are not strictly “protective” in the preventive sense, but they confer relative biological or clinical advantage.

IDH1 R132H Alters metabolism, reduces tumor aggressiveness. It is associated with longer survival and better response to therapy[60]. However, IDH1 R132H represents a somatic mutation (not a germline one) that arises in tumor cells during tumor development, rather than being germline or inherited. This hotspot mutation occurs early in low-grade gliomas (prevalent in 80% of WHO grade II/III cases) and

persists throughout progression to secondary glioblastoma, but it affects less than 5% of primary glioblastomas.

MGMT (O6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that removes alkyl groups from the O6 position of guanine. Promoter methylation of the *MGMT* gene silences its expression, reducing the cell's ability to repair DNA damage caused by alkylating agents such as temozolomide. MGMT promoter methylation is acquired during tumorigenesis and is not inherited. It is found in the tumor DNA, not in the germline. There is no known germline variant that causes constitutional MGMT promoter methylation in glioblastoma.

In very rare cases (e.g. constitutional epimutations), germline methylation of tumor suppressor genes has been reported in other cancers (e.g. *MLH1* in Lynch syndrome), but this is not established for *MGMT* in glioblastoma.

Regarding glioblastoma, no variants nor mutations with a "protective" character have been found. However, HLA-A 32:01 (HLA: human leucocyte antigen A) a germline variant, has been associated with improved survival, although no protective features can be assigned to this variant[61][62]. According to Song et al.[63] HLA-A 32:01 haplotype seems to be associated with risk reduction for glioblastoma occurrence (odds ratio = 0.41). The exact mechanism by which the HLA-A*32:01* variant negatively associates with glioblastoma (GBM) occurrence or improves prognosis is not known. However, it has been suggested that the HLA-A allelic product encoded by HLA-A32:01 is likely to be functionally important in the context of GBM. The beneficial association of HLA-A32:01 with GBM might stem from its role in modulating immune responses against glioblastoma cells because HLA-A32:01 mediates cytotoxic T-lymphocytes responses and natural killer cell function.

This finding may have clinical implications for the development of personalized immunotherapeutic approaches to GBM[64][65][66].

12) Cancer risk in general

Laron syndrome (LS) is a rare, autosomal recessive genetic disorder that was first described by Zvi Laron in 1966[67][68]. It is characterized by short stature, obesity, and other skeletal disorders (dwarfism) and results from the body's inability to effectively use growth hormone (GH), despite having high levels of GH in the blood[69]. This insensitivity is primarily due to mutations or deletions in the growth hormone

receptor (GHR) gene, leading to a defect in the GH/insulin-like growth factor type 1 (IGF-1) signaling pathway.

The main characteristics of LS consist of:

- **Growth Deficiency:** Individuals with Laron syndrome are typically of near-normal size at birth but experience slow growth from early childhood, resulting in very short stature. Adult males may reach a maximum height of about 4.5 feet, while adult females may be just over 4 feet tall[70]
- **Biochemical Profile:** Patients exhibit high serum levels of GH and low concentrations of IGF-1[71].
- **Typical Appearance:** Affected individuals often present with dwarfism, a characteristic facial phenotype, obesity, and hypogenitalism[72]. Affected individuals are close to normal size at birth, but they experience slow growth from early childhood that results in very short stature[73][74].
- **Other Manifestations:** They may also suffer from hypoglycemia, hypercholesterolemia, and sleep disorders. Spinal abnormalities such as cervical spinal stenosis, and degenerative changes of the atlanto-odontoid joint have been reported, making patients prone to neurological morbidity and sleep disorders[75]. One case also reported subclinical hypothyroidism and dyslipidemia. Cardiac abnormalities like patent ductus arteriosus or peripheral vascular disease are rare, but cardiac hypertrophy has been observed after IGF-1 therapy[76].

Interestingly, families with Laron syndrome rarely, if ever, develop cancer. LS is the best known entity of congenital insulin-like growth factor-1 (IGF1) deficiencies. Epidemiological analyses have shown that these patients do not develop cancer, while heterozygous family members have a cancer prevalence similar to the general population[77]. Genome and pathway studies showed that the expression of most of the genes involved in replication control, motility and malignant transformation are decreased in LS.

The growth hormone receptor (GHR) gene codes a transmembrane protein with 620 amino acids. Binding of growth hormone to the receptor induces a conformational change that allows its dimerization which triggers intracellular signaling that leads to growth. GHR mutation generates a protein that is insensitive to growth hormone stimulation.

In addition to having an important reduction of their body mass, mice genetically engineered to carry defective GHR, show a ~40% increase in lifespan and resistance to age-related diseases[78]..

TPCN variants.- The GG genotype in *TPCN2* rs3750965 has been significantly associated with a decreased overall risk of cancer, and genotypes GA/GG were associated with a significantly lower risk of

developing various malignant neoplasms, including melanoma, prostate, mesothelial, and soft tissue cancers [26].

Discussion

No germline mutated gene has been found that can hint towards an hereditary resistance to cancer. On the other hand, many genomic variants have been discovered, showing that certain individuals have a lower susceptibility to cancer. Does this mean that there is no such a thing as hereditary resistance to cancer?

To answer this question we have to analyze the historical background of its opposite, that is hereditary cancer predisposition syndromes.

In 1866, Pierre Paul Broca described a family in which every woman in four consecutive generations developed breast cancer[79].

At the end of the nineteenth century and beginning of the twentieth, Aldred Scott Warthin, a professor of pathology at the University of Michigan, USA made many discoveries, including the giant cells in measles, the benign parotid tumor now known as Warthin tumor, and documented the heritability of cancer[80].

The story of Warthin's findings began in 1895 when his seamstress, told him about the many deaths in her family due to cancer. These tumors were mainly colorectal, gastric, and uterine. Warthin, who was a skilled observer and researcher, followed the medical history of the family for almost twenty years and documented her familial pedigree including the pathological findings. He published this data, along with data from two other "cancer" families, in 1913. He also noted that transmission of the cancer phenotype within the families was consistent with Mendel's autosomal dominant inheritance.

By the 1940s it was clear that there were families in which breast cancer frequency was exceptionally high, sparking the idea of its hereditary nature. In 1946, a Danish surgeon Oluf Jacobsen published a book entitled "Heredity in Breast Cancer: A Genetic and Clinical Study of Two Hundred Probands"[81]. This was one of the earliest systematic investigations into familial patterns of breast cancer. Conducted in Copenhagen, it laid foundational insights into the genetic predisposition to breast cancer.

Jacobsen's study was pioneering in its attempt to correlate family history with breast cancer incidence, analyzing 200 patients (probands) and their relatives. His work predated the discovery of BRCA1/2 genes by decades but anticipated the idea that genetic factors contribute significantly to breast cancer risk.

Jacobsen identified familial clustering of breast cancer cases, suggesting hereditary transmission patterns, and highlighting the need for genetic and clinical surveillance in families with multiple cases. Jacobsen also observed that the average age of patients with “familial” breast cancer was lower than that of sporadic cases, a pattern now recognized in hereditary breast cancer syndromes. Using detailed family trees, he proposed that genetic predisposition could be transmitted across generations, even though the molecular mechanisms and DNA’s role in heredity were unknown at the time of Jacobson’s publication. He emphasized the importance of family history in risk assessment, a concept that remains central to modern oncology.

Jacobsen’s work was ahead of its time and influenced the trajectory of cancer genetics in several ways. His observations supported the hypothesis that germline mutations could underlie familial breast cancer, paving the way for the eventual discovery of BRCA1 (1994) **and** BRCA2 (1995). His emphasis on family history helped establish the clinical value of pedigree analysis, now a cornerstone of genetic counseling. Jacobsen’s insights contributed to the development of risk models (like the Gail and Claus models) that incorporate family history to estimate breast cancer risk.

Jacobsen’s 1946 study is now viewed as a seminal work in hereditary cancer research, bridging clinical observation and genetic theory long before molecular tools were available. His meticulous documentation and analytical approach remain a model for clinical genetic studies.

It was Henry Lynch's turn in 1962 to begin unraveling the tangle of "hereditary cancer" when, as a resident, he encountered a patient with a family history similar to the one published by Warthin. The patient in question had a long family history of deaths from colorectal cancer. The initial diagnosis, obviously, was familial adenomatous polyposis (FAP), but a review of the pathology reports and clinical histories showed no adenomas, which ruled out FAP. Clearly, this was a pathology of a different nature.

This family not only had many cases of colorectal cancer, but also endometrial cancer. In 1966, Lynch published his findings including those of another similar family reported by another team of physicians. However, the genetic nature of this familial disease was not accepted by mainstream science until many years later when the exact molecular pathology could be determined. This condition is now called Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC).

Lynch syndrome is characterized by a malignant colon tumor, usually in the proximal portion of the colon. Other tumors are frequently found in the family and in the same individual, such as those of the endometrium, gastric, hepatobiliary system, ovaries, upper urinary tract, breast, pancreas, and prostate.

In the first half of the 1990s, the genetic nature of Lynch syndrome was confirmed when mutations in MMR (mismatch repair) genes were identified. MMR genes are DNA repair genes and are altered (mutated) in Lynch syndrome.

The proteins encoded by these genes repair errors in DNA replication. However, when they are altered or mutated, they are unable to repair the mismatches produced during replication, resulting in DNA mutations. Sequences in which these mutations are not repaired are present in many of the genes involved in cancer.

In the case of hereditary cancer predisposition, research started from disease, and then it sparked familial investigation and at the end of the way genetic characterization. On the other hand, families without cancer have not been a source of interest or research. There are no registered large population studies of families without cancer. Therefore, there is no available evidence for, or against the possibility of germline mutations that can reduce cancer susceptibility.

Protective genetic variants have been discovered in cancer populations but no research has been directed towards “no-cancer” families. This occurs because these families and/or researchers are usually unaware of the “no-cancer” condition of these families. Therefore, we are in the shadows, and unable to answer the question about the possible existence of germline protection against cancer.

Countries that have an extended and detailed health database that have registered at least three generations would be the best place to search for no-cancer families with an average survival above 70. These families are those that deserve genetic studies that may lead to cancer-protection mutations.

The only “cancer protection” mutation that has been confirmed to decrease cancer risk is that of the germline mutation of the growth hormone receptor gene that causes the Laron syndrome. It has gained significant scientific attention because individuals with this condition appear to be almost entirely immune to cancer[82]. Research, most notably on a large cohort in Ecuador, has shown that despite having higher rates of obesity (a known cancer risk factor), people with Laron syndrome rarely, if ever, develop malignancies[83][84][85][86].

The molecular mechanisms behind this protection are probably related to one or more of the following traits of Laron syndrome:

- **Reduced IGF-1 signaling**: Mimics caloric restriction and downregulates mTOR, promoting autophagy and stress resistance[87].
- **Improved insulin sensitivity**: Despite increased adiposity, GHRKO mice are protected from diabetes.

- **Reduced cell proliferation** and increased apoptosis in precancerous cells.
- **Altered mitochondrial function**: Enhanced oxidative metabolism and reduced ROS production.
- **Reduced inflammation**: Lower levels of pro-inflammatory cytokines.
- **Therapeutic implications**: Targeting GH/IGF-1 signaling is being explored for anti-aging and cancer prevention strategies.

Conclusions

While germline mutations are critical in cancer susceptibility and therapeutic response, the available information does not identify specific germline mutations that actively confer resistance to cancer development. There is evidence that some genetic variants can slightly reduce the risk for specific cancers or improve the therapeutic results. Protective variants are rare and often population-specific. We believe that protective genotypes are underreported and insufficiently investigated.

Answering the question of the title of this paper, we can say that there is no germline cancer resistance genotype with the possible exception of individuals who suffer from Laron syndrome. However, there are genetic variants with a lower risk for cancer. Genetic research on animals, such as the studies on elephants and bats show that cancer protective genotypes are limited to these species and cannot be extrapolated to humans.

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