Review Article

Hereditary Decreased Cancer Risk: Reality or Mirage? A Review

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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 most of them have been thoroughly studied.

While most germline studies focused on pathogenic variants that increase cancer risk (e.g. BRCA1/2, CHEK2 with odds ratio 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. No single genes fully prevent cancer in humans, but specific genetic variants and highly conserved genes across species have been proposed as inducers of reduced risk by enhancing DNA repair, apoptosis, or immune surveillance. Research identified some protective alleles that limit tumor initiation or progression, often acting dominantly at tissue levels. However, most of the publications show controversial results. It is not possible to construct a list of germline variants that confer reduced overall cancer risk, as most identified associations are context-specific (e.g., for certain cancer types, or specific populations) and based on statistical correlations rather than causal mechanisms. Research has uncovered rare protective variants and common polymorphisms with modest effects, often in immune or tumor suppressor pathways. These mechanisms do not fully explain why two-thirds of people, including most heavy smokers, remain cancer-free.

The aim of this review is to summarize the main genetic features that can reduce the risk of developing cancer in general and in some specific cancers as well.

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1. Introduction

Without entering into statistical details, we can roughly say that one third of humans develop a cancer during their lifetime. Approximately 5-10% 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. Another approximately 40% of cancers are related to environmental cancers such as smoking, industrial polluting, UV light, infectious agents, or life style issues such as unhealthy diets, alcohol intake, obesity, among some others [1].

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, some interesting laboratory evidence has been collected in the last ten years, hinting towards a cancer resistant phenotype based on specific hereditary genetic variations. Unfortunately, evidence of a cancer-resistant genotype is poor.

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.

It is important to distinguish three intermingled conditions that may lead to confusions:

1. Hereditary decreased cancer risk: in this case we must separate two different populations
    1. Normal individuals.
    2. Individuals with a hereditary cancer predisposing syndrome that do not develop a cancer.
2. Individuals with cancer in whom an hereditary condition leads to better therapeutic responses.
3. Individuals with cancer in whom an hereditary condition decreases the severity of cancer.

In this review, only the first group, hereditary decreased cancer risk, will be analyzed in depth.

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

2. Animal evidence

► **2.1. Elephants** are the paradigm of a hereditary cancer resistance-like profile [2][3][4]. Abegglen et al. [5] 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’s paradox [6][7]. 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 [8][9]. In elephants this does not happen. Interestingly, elephants have 20 copies (40 alleles) of the TP53 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.

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 substantially 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 [10][11][12][13].

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 [14].

► **2.2. Naked moles** also seem to have cancer resistance features but they seem to be a consequence of mechanisms different from those found in elephants [15][16][17]. 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.

Naked mole-rats evolved over ~31 million years in harsh underground environments, and this long evolutionary trajectory produced a broad suite of cytoprotective mechanisms that help them avoid cancer. These mechanisms include [18]:

Exceptional proteostasis (dynamic regulation of a balanced and functional proteome)

Enhanced DNA repair

Resistance to oxidative stress

Altered cell-cycle regulation.

The emerging consensus is that naked mole-rats do not rely on a single “anti-cancer gene,” but rather a multilayered defense system involving:

Unique extracellular matrix properties

Highly efficient stress-response pathways

Specialized immune surveillance

Chromatin and transcriptional regulation that suppresses oncogenesis.

Hadi et al. [19] showed that the environment of the naked mole-rat’s body prevents the cancer from developing, contradicting previous studies that suggested that an inherent feature of naked mole-rat cells stopped them turning cancerous in the first place. However, there are genetic differences that partially explain the cancer-resistance phenotype in these animals. Naked mole rats exhibit exceptional cancer resistance, and several genes have been identified as contributing to their "anti-cancer" properties. These include tumor suppressor genes like p16INK4a, p27, PDCD5, DKK3, and notably HAS2, which produces the high molecular-weight hyaluronan (HMW-HA) mentioned above [20].

HAS2: Encodes HMW-HA, which accumulates due to slow recycling and triggers p16INK4a-mediated anti-cancer responses [21].

PDCD5 (programmed cell death 5) and DKK3: Show potent cross-species tumor suppression, inhibiting pathways like AKT/mTOR and Wnt/β-catenin more effectively than human/mouse versions. PCDC5 protein is considered an apoptosis-accelerating molecule. PDCD5 positively regulates the TIP60–p53 signaling pathway, enhancing p53-dependent apoptotic responses [22].

p16INK4a and p27: Halt excessive cell division, preventing early tumor development.

► **2.3. Cetaceans**.- Cancer is remarkably rare in whales (and other cetaceans like dolphins and porpoises) compared to what we might expect given their enormous size and long lifespans. This is a classic example of Peto's paradox. A blue whale, for instance, has roughly 1,000 times more cells than a human and can live over 100 years (bowhead whales up to 200+ years), so one might predict a dramatically higher cancer risk. Yet the opposite is true: whales have very low cancer rates [23]. In most wild cetacean populations, cancer prevalence (the proportion of individuals affected) is estimated at 0.7-2.0% based on

necropsy data from stranded or harvested animals. Aggregated studies across species show a mean neoplasia (tumor/cancer) prevalence of around 1.4% (excluding heavily polluted populations).

Cetaceans rank among the most cancer-resistant mammalian groups, often second only to certain other large or specialized species in comparative analyses.

Specific examples include bowhead whales (longest-lived mammals), where cancer is detected in only a few percent of examined individuals (e.g., 3-5% in some subsistence-harvested samples, often benign like hepatic lipomas).

Sporadic cases of cancer do occur across species (e.g., in humpback, fin, sperm, and blue whales), but they are uncommon and not a major cause of mortality in healthy populations.

Tejada-Martinez et al. [24] studied the role of natural selection in the evolution of 1077 tumor suppressor genes (TSGs) in cetaceans. They found that positive selection and duplication of tumor-suppressor genes in cetaceans, was one of the clues to their cancer resistance. The TSGs evolutionary turnover rate (gene gain and loss) was almost 2.4-fold higher in cetaceans when compared with other mammals, and notably even faster in baleen whales.

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. A central discovery is the role of the cold-inducible RNA-binding protein (CIRBP), which was found to be highly expressed in whale fibroblasts and tissues. CIRBP is expressed at dramatically higher levels (up to 100 times more than in other mammals), however, there is no evidence of increased number of copies. Actually, this issue has not been investigated. On the other hand, studies have been performed to quantify gene copy number for TP53, PCNA, HER2, DLG1, and DLG2 in genomic DNA extracted from frozen skin samples of beluga, narwhal and bowhead whales (n=20 each). Results showed that all 3 whale species had more than one copy of PCNA [25].

PCNA plays a role in preventing slippage and therefore it plays a role in decreasing the possibility of mismatch repair [26] and also facilitating mismatch repair [27].

CIRBP enhanced DNA repair efficiency in human cells by promoting both major double-strand break repair pathways and reducing chromosomal abnormalities. When CIRBP was over-expressed in fruit flies, it extended lifespan and increased resistance to irradiation. This protein, that excels at repairing DNA double-strand breaks, when introduced into human cells improves DNA repair accuracy and lowers

mutation rates. This appears central to their cancer resistance and longevity, rather than extra tumor suppressors [28].

This suggests that CIRBP contributes to maintaining genomic stability by protecting DNA ends and supporting efficient repair processes. Unlike species that rely heavily on cell death to eliminate damaged cells, bowhead whales appear to favor faithful DNA repair, a strategy that conserves cell populations and may slow aging [29][30].

► **2.4. 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. [31]. The mechanism in this case is a very efficient immune system using interferon-mediated cell death mechanisms.

A study comparing *Mus spretus* and *Mus musculus* across a skin cancer susceptibility locus shows substantial sequence divergence, supporting the idea that *M. spretus* carries alleles that reduce tumor susceptibility. This aligns with decades of QTL mapping showing that *M. spretus* contributes resistance alleles when crossed with *M. musculus* in skin carcinogenesis models [32]. QTL stands for quantitative trait locus which is a region of DNA that contributes to variation in a quantitative trait, a trait that varies continuously (like height, weight, or cancer susceptibility). It is not a single gene, but rather a chromosomal segment that may contain multiple genes influencing the trait. QTLs help reveal the genetic architecture of complex traits, whether they are controlled by many small-effect genes or a few large-effect ones. Identifying QTLs is often the first step toward finding the actual causal genes.

A 2026 study reports elevated lysosomal mass and enzyme activity in *Mus spretus* fibroblasts.

Because lysosomal autophagy pathways are central to protein quality control, removal of damaged organelles, and suppression of oncogenic stress, this enhanced activity is a plausible mechanism for reduced malignant transformation [33].

Although the plague-resistance study is not about cancer, it demonstrates that *M. spretus* harbors multiple genetic factors that confer unusually strong resistance to lethal biological stressors.

This supports a broader pattern: *M. spretus* has robust innate immune and stress-response pathways, which likely contribute to tumor suppression (e.g., rapid clearance of damaged or pre-malignant cells) [34].

► **2.5. 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 [35][36][37]:

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.

In summary Comparative genomics across bat species reveals significant genetic alterations associated with resistance to infections and cancer. These include modifications in genes involved in immune regulation, stress responses, and cellular homeostasis, and supports the idea that bats evolved a coordinated, multi-pathway defense system, rather than a single anti-cancer gene [38].

► **2.6. Grey squirrels** (Sciurus carolinensis, also known as eastern gray squirrels) are considered "cancer-resistant" relative to many other mammals, particularly in the context of their long lifespan (up to ~24 years in the wild or captivity, far exceeding typical small rodents like mice that live 2-4 years) and small body size.

Grey squirrels exhibit extremely high telomerase activity across nearly all tissues, levels comparable to those in human cancer cells. Telomerase maintains telomeres (chromosome ends), allowing cells to divide more times without senescence. In humans and most mammals, high telomerase is linked to

increased cancer risk because it enables uncontrolled cell proliferation. Yet grey squirrels remain long-lived and cancer-resistant, implying they have evolved unique compensatory mechanisms to counteract this risk [39].

Key observations show that:

1. Slow growth.- Grey squirrel fibroblasts grow much slower in culture (doubling time ~7 days) than compared to human or mouse cells (~2 days). This slow division rate likely reduces the accumulation of mutations that could lead to cancer.
2. Tight cell-cycle regulation.- Their cells appear to have robust controls (possibly involving tumor suppressors like Rb and p53) that limit rapid growth and mutation buildup, preventing the initiation of tumors.

Unlike naked mole rats (early contact inhibition via high-molecular-weight hyaluronan) or blind mole rats (interferon-mediated cell death), grey squirrel cells do not show these traits. This suggests a distinct, still not fully identified anti-cancer adaptation [40][41].

Despite high telomerase, grey squirrels are not completely immune to oncogenic transformation in experimental settings (e.g., when artificially introduced with certain oncogenes), but in nature, their combination of slow proliferation and other safeguards keeps cancer incidence remarkably low.

3. Hereditary cancer resistance in humans?

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 gene variants 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 down-regulate oncogenic pathways

Variants that enhance immune surveillance

Variants that reduce inflammation (chronic inflammation increases cancer risk)

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.

3.1. 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[42]. 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 (see below). (rs stands for reference SNP cluster ID. This is the standard naming system used in genetic databases to uniquely identify a specific **single nucleotide polymorphism (SNP), the most common type of genetic variation where a single DNA base (A, T, C, or G) differs between individuals at a particular position in the genome).

Certain p53 mutations, such as R273H, may sensitize tumors to immunotherapy despite loss of suppressor function [43]. 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 were proposed as giving protection against specific cancers by enhancing DNA repair, modulating immune responses, or inhibiting tumor growth pathways.

4. Hereditary mechanisms that enhance DNA repair

Variants that enhance DNA repair are much rarer than variants that impair it, and the literature is sparse. Still, several human polymorphisms have been associated with higher DNA repair capacity or reduced chromosomal damage in population studies. The evidence is mostly correlative, but it does point to a set of "protective" alleles that primarily involve germline genetic variants, such as single nucleotide polymorphisms in DNA repair genes that boost repair efficiency and may confer protection against cancer or other genomic instability-related diseases. Unlike well-known hereditary syndromes with defective repair (e.g., xeroderma pigmentosum), enhanced repair variants are subtler and often identified through association studies linking them to reduced cancer risk or improved survival [44][45].

Evidence showing a hereditary better DNA repair system is often inferred from associations with reduced cancer risk (as improved repair reduces mutation accumulation leading to cancer). However, findings across studies are sometimes inconsistent due to population differences, environmental factors, and functional assays. Some variants supposedly involved in "better" DNA repair are described in Table I.

Gene	Variant	Effects
XPA	rs1800975 (G23A polymorphism)	The 23G allele (often considered the ancestral allele) has been associated with higher DNA repair capacity (DRC) in the nucleotide excision repair (NER) pathway.
XRCC1	rs1799782 (Arg194Trp)	The minor allele (Trp, or T) has been linked to decreased overall cancer risk, suggesting potentially enhanced BER efficiency.
XRCC1	rs25487 (Arg399Gln)	Some studies link the Arg allele to higher repair capacity, but evidence is inconsistent.
ERCC1	rs11615 T19007C	This is a silent polymorphism that may influence mRNA stability or translation efficiency, potentially enhancing NER.
DNA-PKcs	rs12334811 and Rs8178085	This is not really a protective variant; however it is associated with better therapeutic response due to lower repair capacity in lung adenocarcinoma. No risk reduction.
hOGG1	rs1052133	Some studies show protection against Wilms tumor. However, most other studies found risk increase.
FEN1	rs174538, rs4246215	Associated with risk reduction of Wilms tumor in Chinese population.

Table 1. Some gene variants proposed to have possible increased DNA repair abilities

XPA rs1800975

This variant is a common promoter-region polymorphism in the XPA gene, a core component of nucleotide excision repair (NER). It lies in the 5′ regulatory region, and it has been hypothesized to influence XPA expression and thus NER capacity.

In a meta-analysis of lung cancer studies (7 populations, 1,913 cases and 1,882 controls), the G/G genotype showed a protective effect against lung cancer (odds ratio [OR] = 0.75), and the G/A genotype had an OR of

0.73. This protective effect is supported by functional studies showing that individuals with at least one G allele have significantly higher DNA damage repair capacity in healthy subjects [46].

However, some studies report conflicting associations, such as an opposite relationship with base excision repair (BER) activity in peripheral blood mononuclear cells (PBMCs), where the A allele was linked to improved NER upon dietary intervention in individuals with multiple low-activity alleles. Overall, the evidence leans toward the G allele enhancing repair efficiency, particularly in NER. A 2020 integrative analysis of 71 case–control studies found that rs1800975 is associated with increased overall cancer susceptibility, although the effect size varies by cancer type and population [47].No clear consensus has been reached on the *XPA* gene rs1800975 polymorphism and lung cancer risk in a meta-analysis of 11 studies [48].

At this point, due to conflicting studies, “protective” effects of XPA rs1800975 are not proved and require further research.

XRCC1 rs1799782

In a large population-based study [49] (3,620 cases and 2,296 controls), carriers of the minor allele had a >25% lower risk of cancer (per minor allele OR = 0.74). Associations in the direction of decreased risk were observed for 12 of 15 cancer types. This SNP is in high linkage disequilibrium (R^2 = 0.99) with rs3213344, which showed similar protective effects (OR = 0.73).

Epidemiological data support a protective role against cancers like prostate, breast, and lung in some populations. However, evidence is mixed: in breast cancer patients, the Trp allele was associated with increased risk of adverse radiotherapy response (OR = 1.98), implying potentially lower repair capacity in response to radiation-induced damage. This discrepancy may reflect context-specific effects (e.g., cancer prevention vs. therapy response). The study showed protective effects in some populations, no effects or increased risk in others. The study seems to be strongly influenced by environmental exposures and ethnic background and type of tumor.

The study showed protective effects in skin cancer which was confirmed in Korean population [50]; increased risk in oral and thyroid cancer [51]; it was inconclusive regarding lung cancer [52].

Therefore, this gene variant represents an example of a context-dependent DNA repair polymorphism [53] [54]. For example, a study by Liu and Xue [55] suggested that the C allele of XRCC1 decreased thyroid cancer

risk in 18% in Chinese population but there were no significant associations among Caucasians under all genetic models.

In conclusion the results are highly controversial.

XRCC1 rs25487

rs25487 is a **G>A** substitution in **XRCC1**, producing an Arg→Gln change at codon 399. This residue lies in a region important for protein–protein interactions in the base excision repair (BER) pathway. This can lead to altered DNA repair capacity. The Gln variant often impairs XRCC1's interactions with repair enzymes like PARP1 and ligase III, reducing BER efficiency and increasing genomic instability [56]. However, effects vary: some assays show minor variants with higher DNA adduct levels, linking to elevated mutagenesis risk.

It was proposed as a "protective" variant, however it was associated with increased cancer risk in functional analyses. A large meta-analysis of 10,846 cases and 11,723 controls found that Arg399Gln increased breast cancer risk in the American population [57]. This is another example of context-dependent DNA repair polymorphism: increased risk for breast cancer, inconclusive results for prostate cancer [58] and decreased risk for skin cancer.

ERCC1 rs11615 (C>T)

ERCC1 is a core component of nucleotide excision repair (NER) where the rs11615 variant (C>T) affects mRNA stability, ERCC1 expression and NER efficiency. The T allele induces reduced ERCC1 expression which increases susceptibility to cancer, not protection.

The C/C genotype showed a suggestive protective effect against lung cancer in a meta-analysis (OR = 0.72, 95% CI = 0.46-1.11), suggesting a 28% risk decrease in lung cancer, though not statistically significant [59]. For example the confidence interval (0.46-1.11 crosses the 1.0 threshold., thus indicating limited statistical power.

The fact that this paper establishes a "suggestive" protection, it is not statistically significant and it is not consistent with other studies that show increased risk for cervical and lung cancer in some populations. The overall evidence points to context-dependent risk rather than universal protection.

Other systematic reviews suggested that *ERCC1* rs11615 exerts a more profound effect on the susceptibility of non-smokers to lung cancer than that of smokers [60].

Most studies show increased cancer risk, no effect, or gene–environment interactions, not protection. It has increased risk for cervical cancer in Chinese population [61]. Khalouei et al. found risk increase for lung cancer with ERCC1 rs 11615 variant in Iranian population [62]. Therefore, ERCC1 rs11615 cannot be considered a protective variant.

DNA-PKcs rs12334811 and rs8178085

In lung squamous cell carcinoma, the GG (rs12334811) and AA (rs8178085) genotypes were "good" genotypes associated with greater radio-chemotherapy efficacy, but this implies lower repair (increasing sensitivity to treatment) rather than enhanced efficiency for cancer prevention. Protective effects against cancer would require further validation. These variants do not seem to exert protective effects.

hOGG1 (rs1052133)

hOGG1 (rs1052133) refers to a common single nucleotide polymorphism in the human 8-oxoguanine DNA glycosylase 1 gene, specifically a C>G base change in exon 7 (Ser326Cys substitution). This variant has been extensively studied in the context of DNA repair efficiency and cancer risk, particularly relevant to oxidative DNA damage in hereditary cancer genetics. hOGG1 encodes a bifunctional DNA glycosylase critical for base excision repair (BER), excising 8-oxoguanine (8-oxoG), the most prevalent oxidative lesion, from nuclear and mitochondrial DNA to prevent G-to-T transversions. The Ser326Cys variant (Cys allele) shows modestly reduced repair activity under oxidative stress compared to wild-type Ser326, potentially accumulating mutations.

However hOGG1 (rs1052133) is a conflictive variant: across cancers, the evidence is mixed and cancer-type–specific, with several studies showing increased risk, some showing no association, and very few suggesting protection [63]. While the rs1052133 variant showed protective function against Wilms tumor and head and neck carcinomas [64] in respective populations, as mentioned above, it has also been implicated in increased risk of various other cancers.

Therefore, the available evidence does not support rs1052133 as a universally protective anti-cancer variant. Across cancers, the direction of effect is inconsistent, and several meta-analyses show increased risk, not protection. It increased risk for hepatocellular carcinoma in Caucasians [65], for prostate cancer in Chinese population [66], and overall cancer risk [67].

FEN1 (Flap endonuclease 1) rs174538, and rs4246215

FEN1 polymorphisms rs174538, and rs4246215 are considered to increase cancer risk by decreasing base-excision repair efficiency. However, a case-control study of 145 Wilms tumor cases and 531 controls in Chinese population found significant protective associations. For rs174538 (A>G, promoter), the AG/GG dominant genotype had an adjusted OR of 0.66, and GG recessive OR=0.54. For FEN1 rs4246215 (dominant) adjusted OR was 0.55 [68].

The authors evaluated several BER-pathway genes, including FEN1, OGG1, XRCC1, and others, in relation to Wilms tumor risk. rs174538 showed significant decrease of Wilms tumor risk and rs4246215 was also associated with risk reduction in the pediatric population. This protective effect is specific to Wilms tumor. In adults and across other cancers, meta-analysis showed increased cancer risk for both. This si an example of cancer-type-specific genetic effects.

Wilms tumor is a pediatric embryonal tumor, with biology very different from adult carcinomas. Adult cancers are not.

Wilms tumor arises from nephrogenic rests, which are embryonic kidney precursor cells that failed to differentiate properly. These cells have:

high proliferation;
unique epigenetic programs;
different DNA-repair priorities
different apoptotic thresholds;
slightly reduced FEN1 can increase replication stress and thus triggering p53-mediated apoptosis, resulting in fewer nephrogenic rests survival.

In contrast, adult cancers arise in:

fully differentiated tissues;
with accumulated environmental DNA damage;
under chronic oxidative and mutagenic stress;
adult cells tolerate replication stress better and do not undergo apoptosis as readily.

The same DNA-repair perturbation can have opposite effects in these two biological contexts.

Variants that slightly reduce FEN1 expression or alter BER activity may:

Reduce proliferation of nephrogenic precursor cells

Alter developmental DNA repair dynamics

Shift susceptibility in a way that is *protective* in childhood but *harmful* in adult tissues.

The explanation above is based on the paper by Zheng et al. (2007) [69] that shows that partial FEN1 loss causes replication stress and p53-mediated apoptosis in rapidly dividing cells. Severe FEN1 loss, on the other hand is embryonic lethal at the blastocyst stage [70],[71].

FEN1variants in adults and in relation to other tumors increase cancer risk:

FEN1 rs174538 (-69G>A): Increases cancer risk in lung, breast, esophageal, gastric, liver, colorectal, gallbladder, glioma, leukemia, and oral cancer [72][73][74].

FEN1 rs4246215 (4159G>T): Increases cancer risk. This SNP is located in the 3′-UTR of *FEN1* and affects mRNA stability and expression. Reduced or dysregulated FEN1 activity leads to impaired long-patch base excision repair, which increases genomic instability — a mechanistic direction fully consistent with higher cancer susceptibility.

From these analysis of the role of DNA repair genes variants that supposedly have a protective role we can conclude that the only reliable evidence is that of FEN1 variants that reduce Wilms tumor risk in children in certain populations. However, this variants probably increase cancer overall risk in adults.

5. Hereditary mechanisms that down-regulate oncogenic pathways

Gene	Mutation	Effects
AURKB	Loss of function	Germline loss of function of this proto-oncogen is the only well identified protector in a pan-cancer context.
PPP1R15A (GADD34)	Loss of function	This is an essential gene in the integrated stress response and its loss of function has been proposed as protector.

Table 2. Down-regulation of oncogenic pathways

► **5.1. Aurora kinase B** involved in mitosis and cytokinesis, have been associated with protection 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 [75].The study used gene-based burden tests and 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. 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 [76][77][78]. 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.

However, AURKB germline loss seems to be a controversial issue, because it can be lethal or cause severe developmental diseases.

Aurkb-/- embryos die at the morula/blastocyst stage. These embryos show severe chromosome segregation defects and no viable germline LOF is possible [79]. Therefore AURKB germline LOF is lethal, not protective. Only somatic inhibition of Aurora kinases is protective against cancer, and this is a therapeutic effect, not a hereditary protective trait.

► **5.2. PPP1R15A** encodes **GADD34,** a regulatory subunit of protein phosphatase 1 (PP1). It is induced by ER stress, oxidative stress and DNA damage. Interestingly, PPP1R15A has pro-apoptotic effects in severe stress while it is anti-apoptotic in moderate stress. In the cancer context this protein has pro- and anti-tumoral effects. It has a tumor suppressive role by promoting apoptosis. Loss of function of the gene increases tumor growth, enhances stress tolerance in malignant cells and promotes chemoresistance. However. Its over-expression has a tumor promoting role. As a context-dependent gene, PPP1R15A loss of function can have a protective effect in cancers that rely on high protein synthesis and stress adaptation, such as glioblastoma and pancreatic ductal adenocarcinoma. At the same time, its loss of function is pro-tumoral on those cancers where apoptosis depends on GADD34 induction, such as colorectal cancer and hepatocarcinomas.

There are no known germline PPP1R15A variants that are proven to reduce cancer risk in humans.

This is probably related to the fact that loss-of-function is not tolerated enough in humans to appear as a benign protective variant. PPP1R15A knockout mice are viable but stress-hypersensitive, and complete LOF in humans is extremely rare [80][81].

All the evidence supports PPP1R15A as a stress-response gene, not a hereditary cancer-protection gene.

6. Hereditary mechanisms that modulate immune vigilance or response

Germline variants in immune-related genes like IFIH1 and TMEM173 (STING1) modulate interferon signaling, potentially aiding anti-tumor immunity [82]. IFIH1 variants (rs35667974) have protective effect regarding autoimmune diseases [83] but there is no evidence of being protective against cancer.

Importantly, there are genes than increase immunosurveillance.

6.1. Germline Immunoglobulin gene variations can improve antigen recognition, antibody maturirty and more effective immune responses [84]. Germline V gene variations are increasingly being recognized as an important player in an effective immune response, which might lead to varying disease susceptibility. Research in this sense has been focused in infection and autoimmunity, however, we believe is also valid for cancer.

Immunoglobulin germline alleles (IGHV, IGKV, IGLV) increase antigen recognition, improve B cell responses and may enhance tumor antigen detection.

IGHV germline alleles (immunoglobulin heavy chain variable region genes) determine antibody binding strength and epitope preference. This has been found in relation to SARS-Covid virus [85] where some IGHV alleles generate antibodies that bind conserved viral epitopes, making individuals less susceptible to immune escape. We may presume that these alleles can have a similar protective effect in cancer. This needs further experimental confirmation.

IGVH germline polymorphisms have been found to modulate B-cell receptor repertoires [86].

These two findings do not guaranty protection against cancer, although they suggest it. Certain IGHV alleles are associated with better outcomes in B-cell malignancies. Messmer et al. [87] showed that IGHV1-69 germline polymorphism modulates clinical outcome in chronic lymphocytic leukemia. Patients with specific IGHV1-69 alleles had longer time-to-treatment and better survival. Furthermore, Hamblin et

al. [88] found that CLL patients mutated IGHV alleles had a better outcome that those lacking a germline mutation. Similar benefits were found with IGHV3-21 allelic variant [89][90].

The study by Setliff et al. [91] introduced a high-throughput platform for linking BCR sequences to antigen specificity, and performed the first large-scale demonstration that germline IGHV alleles encode inherent epitope preferences, and some IGHV germline configurations produce more resilient, broadly reactive antibodies.

In spite of the references above, there is no direct proof of general cancer protection by IGVH germline polumorphisms. Furthermore, IGHV lacks established links to lower cancer incidence across populations. Antigen-driven selection produced by IGVH is not a proxy to germline protection from cancer onset. No studies show germline IGHV polymorphisms decreasing cancer risk or incidence; associations are prognostic within cancers like CLL, not preventive. Related cytokine SNPs (e.g., TNF-α rs361525) may modulate risks for specific cancers like lung but are not IGHV variants [92].

IGKV genes encode the variable region of immunoglobulin kappa light chains, with germline polymorphisms influencing B-cell receptor diversity and antibody responses. These variants affect immune repertoire but show no causal link to reduced cancer risk in population studies; any associations are typically prognostic or therapy-related (e.g., IGKV3 as vaccine targets in B-NHL). In contexts like CLL or AML, IGKV usage or somatic changes may influence progression or migration (e.g., promoting AML cell motility), but germline polymorphisms lack protective effects on incidence [93].

IGLV polymorphisms: IGLV encodes the variable region of immunoglobulin lambda light chains, with germline polymorphisms shaping B-cell receptor diversity similar to IGKV/IGHV. These variants influence immune responses but lack evidence for reducing cancer risk in population studies; any links are to immune modulation or repertoire effects, not prevention.

6.2. Germline variants in immune-response genes that modify cancer penetrance

Inherited variation in immune-response genes can alter cancer risk, age of onset, tumor immune microenvironment, and even response to immunotherapy. There *are* studies showing that germline immune-response variants modify cancer risk, tumor immune microenvironment, and immunotherapy response. Germline variants influence immune infiltration, antigen presentation, and tumor microenvironment architecture across cancers [94].

6.3. Germline DNA damage response variants that improve response to immunotherapy

Germline mutations in DNA damage response genes act as predictive biomarkers of immune checkpoint inhibitor efficacy [95]. However, this is not cancer risk reduction.

6.4. The HLA system

There are variants (alleles or genotypes) in the Human Leukocyte Antigen (HLA) system associated with protection against certain cancers. The HLA genes, part of the major histocompatibility complex (MHC), play a key role in immune surveillance by presenting antigens (including tumor-derived ones) to T cells, helping the immune system recognize and eliminate cancerous cells. Research shows several protective associations:

6.4.1. HLA heterozygosity (having different alleles at HLA loci) often provides a protective effect, likely due to greater diversity in antigen presentation, improving the immune system's ability to detect tumor cells. This is described as a "heterozygote advantage."

For lung cancer, germline heterozygosity at HLA class II loci (especially in smokers) is linked to reduced risk. Similar protective effects from heterozygosity appear in colorectal cancer (both class I and II loci) and some other solid tumors like head and neck cancer.

Higher HLA diversity in general correlates with lower risk for various cancers, including those with high tumor mutation burden.

Specific alleles have been identified as protective in certain contexts:

HLA-A* 02:01 is associated with decreased risk and longer survival in pancreatic ductal adenocarcinoma (PDAC), particularly in tumors with certain mutations [96]. Importantly it enhances KRAS-derived neoepitopes binding. It was also suggested that A*02:01 carriers increased CD8+ immunosurveillance.

HLA-B* 44:02 showed a protective association (lower prevalence in tumors) in analyses of solid malignancies [97]. The 2023 study analyzed HLA-A, B, and C alleles from 179 solid malignant tumors, primarily in Caucasian Americans. It identified HLA-B*44:02 as protective overall, with a prevalence ratio (PR) of 0.36 compared to NMDP-listed frequencies, indicating underrepresentation in tumors versus the general population. The B44 supertype (which includes B*44:02) has been associated with enhanced antitumor immune responses in specific contexts, particularly in immune checkpoint blockade (ICB)-treated tumors, particularly NSCLC and melanoma [98]. Protective effects may stem from enhanced

neoantigen presentation or T-cell responses, though mechanisms in solid tumors need further validation due to small sample sizes [99].

Older studies noted protective alleles like HLA-DQB1*03 for hepatocarcinomas and cervical cancer [100]. HLA-DRB1*11has been reported as a protective allele in at least one cancer type, breast cancer in a case-control study [101].

Broader analyses of many HLA alleles across multiple cancers often find a preponderance of protective effects (especially for HLA class I alleles) over susceptibility effects for numerous cancer types.

These protective effects stem from better immune recognition of cancer cells, though they vary by cancer type, population (e.g., ancestry), and environmental factors like smoking. Note that some HLA variants increase risk for certain cancers or impair immunotherapy response (e.g., HLA-A* 03 linked to poorer outcomes with checkpoint inhibitors).

This area is active in research, particularly for understanding cancer risk, prevention, and tailoring immunotherapies (like checkpoint inhibitors or personalized vaccines)

7. Protection against specific cancers

7.1. Leukemia

Agarwal et al. [102] 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.

Clonal hematopoiesis is the expansion of a blood-cell lineage that carries a **somatic mutation** in a hematopoietic stem cell. That means that single mutated stem cell in the bone marrow gains a fitness advantage and produces a disproportionately large fraction of circulating blood cells, without meeting criteria for leukemia or other hematologic malignancies.

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 stem cell 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.

7.2. 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 [103]. 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). However, this does not mean that it decreases cancer risk.

7.3. 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 [104]. 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). This finding does not decrease the risk of SCLC.

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 [105].

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 [106].

TP63 (3q28 locus) variants have been associated with reduced lung cancer risk in East Asian never-smokers, possibly via epithelial homeostasis [107].

Telomere maintenance.- Protective alleles may preserve telomere length and genomic stability reducing transformation risk [108].

Genome wide association studies identified GPC5 (Glypican-5) gene variants as protective in never-smokers by inhibiting cell proliferation in lung tissue. GPC5 is a tumor suppressor gene. However, other GPC5 variants (particularly regulatory SNPs in the 5′ upstream region) increase risk. Therefore GPC5 is not uniformly protective [109]. Table 3.

Variant/region	Risk	Evidence	Ref.
rs2352028	Increased	GWAS and meta-analysis	[110]
5′ upstream variants	Increased	Meta-analysis	[111]
Unnamed rare germline mutation c.776C>T variant	Increased	Lung adenocarcinoma affected famiglie. Exosome sequencing.	[112]
GPC5 enhancing variants	Likely protective	Rs2719217 and rs4976143 variants are considered protective against cancer in non-smokers	[113] [114]

Table 3. Increased and decreased risk with GPC5 variants

GPC5 suppresses lung adenocarcinoma tumors primarily through inhibiting key oncogenic signaling pathways like Wnt/β-catenin and receptor tyrosine kinases (RTKs), alongside regulating gene expression and cellular processes. GPC5, a cell-surface heparan sulfate proteoglycan, binds Wnt3a extracellularly, preventing its interaction with Frizzled receptors and subsequent β-catenin stabilization, nuclear translocation, and transcription of proliferation genes. Overexpression reduces tumor growth, migration, and invasion in vitro and xenografts; hypermethylation silences GPC5, abolishing this suppression [115].As a membrane protein, GPC5 diminishes phosphorylation and expression of ERBB2/ERBB3 and RYK, critical RTKs in lung tumorigenesis, likely via heparan sulfate-mediated modulation of ligand binding or trafficking. This inhibits downstream PI3K/AKT and MAPK signaling, curbing proliferation [116].

1) 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 Chaudhuri.

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 [117].

It was suggested that certain BRCA1 variants could have a protective effect against cancer. However this does not seem correct. 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 [118].

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 [119].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 [120].Pharmacological agents like Sephin1 inhibit PPP1R15A and show antitumor effects in models of liver fibrosis-associated cancer by reducing immunosuppressive myeloid-derived suppressor cells.

Downs et al. [121] studied gene variations between pairs of cancer patients and non-cancer familial members that inherited the same BRCA1 mutation. They found that those that did not develop a cancer

harbored a common “beneficial” variant that seemed to prevent cancer development and reached the conclusion that the beneficial variant could play a role in incomplete penetrance.

They found that “*a single-nucleotide polymorphism, rs3735400 located in ANLN gene, which plays an essential role in controlling cytokinesis and is often found to be overexpressed in cancer. The carriers of this variant had lower cumulative risk of developing breast cancer.*” This finding shows how a genetic variant of ANLN, rs3735400, was able to reduce BRCA1 penetrance. Paradoxically, the ANLN gene encodes anillin, an actin-binding protein critical for cytoskeletal dynamics. It plays essential roles in cytokinesis by stabilizing the contractile ring via RhoA interaction and supports cell migration. ANLN overexpression promotes proliferation, migration, and poor prognosis in lung, breast, and other cancers via cytokinesis dysregulation and RhoA activation. Knockdown induces G2/M arrest and reduces tumor growth [122].

2) Cervical cancer

Allele HLA-DQB1 rs55986091 A offers protection against cervical cancer, likely through better viral antigen handling [123].

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 [124].

3) 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 [125].

► 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** [126], 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 [127]. 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** [128].

► The *P2RX4* rs25644 allele GG has been associated with a **low risk of cancer recurrence** in patients with prostate cancer (26 Alharbi, 2021).

► Heterozygotes for the minor allele of rs2302427 in EZH2 show significantly reduced prostate cancer risk (OR 0.63) [129].

► The VEGF -1154 A allele has been linked to lower prostate cancer risk in some studies [34 breyer].

► The minor allele of rs1567669 at NKX3-1 also confers protection among heterozygotes (OR 0.71) [34 breyer].

4) 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 [130].

5) 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 [131].

KLF5 in 13q22.1 is a gene with tumor suppressor activity. Variations of this gene that increase its expression have been found [132]. 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

6) 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 [133](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 [134].

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 [135]. **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 [136][137].

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 [138].

7) Pancreatic cancer

Although most germline mutations (e.g. in *BRCA1/2*, *PALB2*, *ATM*) increase pancreatic cancer risk, some variants may offer relative protection [139]:

SPINK1 N34S variant: While Serine Peptidase Inhibitor Kazal Type 1 (SPINK1) N34S variant is associated with acute and chronic pancreatitis [140][141], 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 [142][143]. 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.

8) 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 [144]. 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 [145][146]. According to Song et al. [147] 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 [148][149][150].

9) Cancer risk in general

Laron syndrome (LS) is a rare, autosomal recessive genetic disorder that was first described by Zvi Laron in 1966 [151][152]. 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 [153]. 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 [154]
- **Biochemical Profile:** Patients exhibit high serum levels of GH and low concentrations of IGF-1[155].

- **Typical Appearance:** Affected individuals often present with dwarfism, a characteristic facial phenotype, obesity, and hypogenitalism [156]. Affected individuals are close to normal size at birth, but they experience slow growth from early childhood that results in very short stature [157][158].
- **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 [159]. 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 [160].

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 [161]. 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 [162].

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].

8. Discussion

No germline mutated gene has been found that can hint towards an hereditary resistance to cancer. On the other hand, many genomic variants with SNPs have been discovered, showing that certain individuals have a lower susceptibility to certain cancers.

Lets analyze real 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 [163].

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 [164].

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" [165]. 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 real interest or research. There are only a few large population studies of

families without cancer. Therefore, there is no sufficient evidence available 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. 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.

Early work [166] proposed studying cancer-resistant individuals or families, drawing from animal models where low-tumor strains resist grafts from high-tumor lines, suggesting heritable resistance genes beyond chance. Human efforts include:

Super-resistant cohorts: Analysis of long-lived smokers (e.g., >90 years cancer-free) via whole-genome sequencing to find protective LoF variants, as in deCODE's identification of AURKB and PPP1R15A from large biobanks contrasting cases vs. controls.

Family-based designs: Creighton University's Hereditary Cancer Center examines risk heterogeneity in high-risk families (e.g., Lynch syndrome), where some sub-families show attenuated penetrance, hypothesizing modifiers or protective alleles [167].

Searching for cancer protection genes or SNP variants is based on genome-wide association studies (GWAS) that can identify genetic variants associated with specific diseases or conditions.

GWAS scan the entire genome of many individuals to find SNPs, small, common variations in a single DNA building block, that occur more frequently in people with a particular trait or disease than in those without it. These studies are largely hypothesis-free, meaning researchers don't start with specific genes in mind; instead, they test hundreds of thousands to millions of SNPs across the genome in an unbiased way. The core idea relies on the "common disease, common variant" hypothesis: many complex traits (like type 2 diabetes, height, schizophrenia, or breast cancer risk) are influenced by numerous common genetic variants, each with small effects.

GWAS steps

1. Sample collection: Researchers gather two groups (or more):
    - Cases: individuals with the disease/trait.

- Controls: similar individuals without the disease/trait.

2. Genotyping: Using high-throughput arrays (like SNP chips from Illumina or others), millions of SNPs are measured in each participant. Imputation can fill in missing data based on linkage disequilibrium (LD), where nearby variants are inherited together.
3. Statistical analysis: For each SNP, a statistical test (often logistic regression for binary traits like disease presence, or linear regression for quantitative traits like height) checks if the allele frequency differs significantly between groups.

   The key metric is the p-value, with genome-wide significance typically set at $p < 5 \times 10^{-8}$ (a strict threshold to account for multiple testing across millions of SNPs, often via Bonferroni correction or similar methods).

   Results are visualized in a Manhattan plot, where the x-axis shows chromosomal position and the y-axis shows $-\log_{10}$(p-value). Peaks indicate associated loci.
4. Post-GWAS steps: Associated SNPs often tag regions rather than being causal themselves. Follow-up includes:

   Fine-mapping to pinpoint causal variants.

   Functional studies (e.g., eQTL analysis) to understand biological mechanisms.

   Polygenic risk scores (PRS) to combine many variants for individual risk prediction.

GWAS permits the identification of thousands of loci for complex traits, revealing shared genetics across diseases (genetic correlations). Large-scale meta-analyses (hundreds of thousands to millions of participants) have dramatically increased power. Sequence-based GWAS capture rare/low-frequency variants. Larger sample sizes and meta-analyses uncover more loci.

However, most associations have small effect sizes. Often explain only a fraction of heritability.

GWAS identifies associations, not direct causation.

Integrating GWAS with single-cell data, and network approaches have expanded its utility to include biological pathways and drug targets. GWAS have transformed our understanding of complex genetics since the mid-2000s, with databases like the GWAS Catalog (from EMBL-EBI) cataloging tens of thousands of associations. They remain foundational for uncovering the genetic basis of human variation and disease.

The only “cancer protection” mutation (meaning that is not a variant) 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 [168]. 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 [169][170][171][172].

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 [173].

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.

There is no such a thing as a cancer protection gene. There are gene variants that produce a subtle protection against specific cancers or sometimes in specific contexts (e.g. non-smokers), or in specific population groups. Humans do not have 20 copies of the TP53 gene as elephants, or slow cellular growth like gray squirrels, or a highly active p53 systems as microbats.

Protective gene variants are difficult to find and many times their activity is controversial. Wilms tumor has a lower risk in one OGG1 variant carrier. However, this benefit is restricted to this tumor and to children at the price of a higher cancer risk in adult life.

On the other hand, the population carrying the “protective” variant is scarce. Furthermore, the protection is not absolute, meaning that protection is not against all cancer, but limited to one or a few tumors, and in spite of the variant, the carrier is not immune to the cancer.

9. Conclusions

While germline mutations are critical in cancer susceptibility and therapeutic response, the available information does not identify a specific germline gene mutation that actively confers resistance to cancer development in general. In this aspect hereditary cancer resistance is different from hereditary cancer susceptibility.

On the other hand. there is evidence that some hereditary genetic variants can slightly reduce the risk for specific cancers or improve the therapeutic results. Protective variants are rare and often population- and tumor-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 not a single gene germline cancer resistance genotype that “protects” against cancer in general, with the possible exception of individuals who suffer from Laron syndrome. However, there are hereditary genetic variants with a lower risk for specific tissues cancer risk. 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. Undoubtedly, an efficient immunosurveillance and DNA repair mechanisms will reduce the risk for cancer and they are probably present in old age-cancer free populations. The low prevalence of the known hereditary protective variations precludes these findings to be considered the primary cause of two third of cancer-free population. It is quite possible that there are other hereditary mechanisms playing a role which are unknown as yet.

A “better” immune system and surveillance seems to play an important role in many protective variants. On the other hand, the proposed “better” DNA repair system of some genetic variants, do not show that this mechanism is operative in most of the protective variants.

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