

# Variation of Cancer Risk from Twin Studies: Is It Mainly Due to ‘Bad Luck’?

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## Conclusions

- Cancer heritability was estimated to be moderate for total cancer and majority cancer types from twin studies.
- Certain cancer type, such as prostate cancer still shows high inheritable genetic risks (*heritability*).
- Environment has great contribution to some cancers, such as smoking related cancers.
- Gene mutations attributed from hereditary was estimated to be low (Tomasetti et al, 2017), then where does the remaining heritability go?

## Introduction

There have been various theories developed since last century, yet cancer etiology remains obscure. While geneticists and biologists tried to understand cancer developing mechanism through sequencing and experiments in the laboratory, epidemiologists conducted twin studies and estimated genetic and environmental origins of cancer.

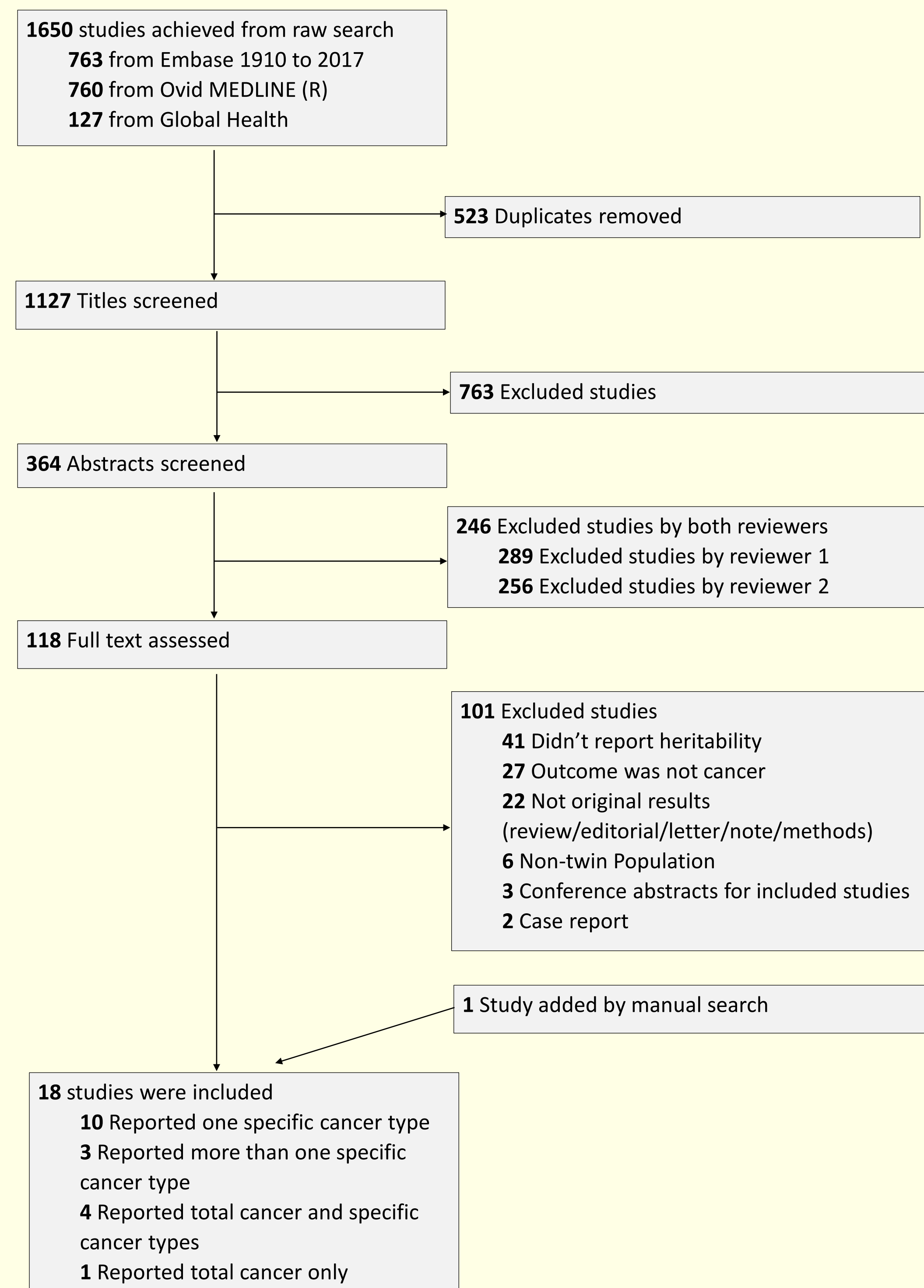
In twin study, variation of cancer can be explained by three components: additive genetic (heritability), shared environment, and unshared environment (the residue, ‘bad luck’).

In this study, we reviewed the literature of twin studies providing heritability estimates of cancers to explore the causes of cancer, and conducted a META analysis on available data.

## Methods

Data were retrieved from twin studies published in English from 1947 to September 2018 by an electronic search. We performed narrative review on the reported heritability of cancers. META analysis was done for specific cancer types by pooling available data and employing R package OpenMx (Neale et al. 2016).

Figure 1. Flow of Studies Through the Review Process



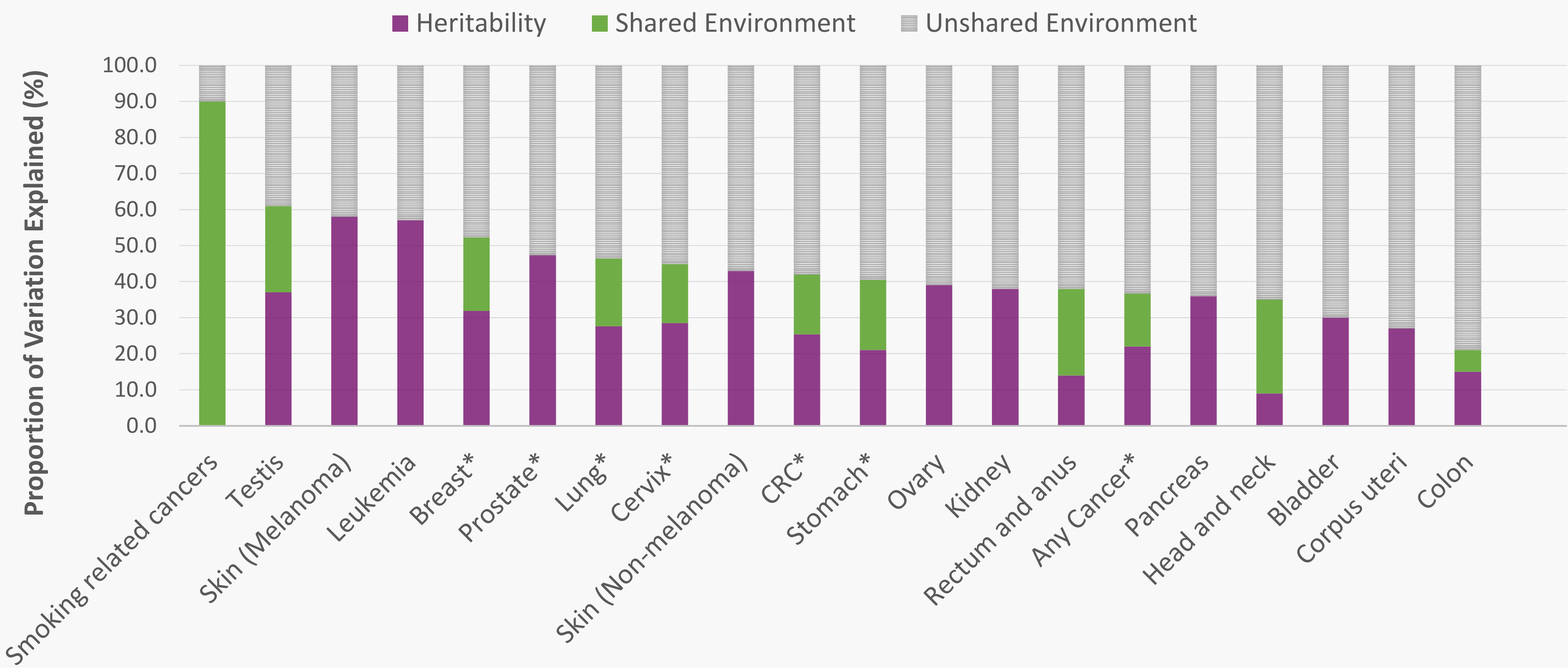
## Findings

- META analysis was conducted for total cancer and six cancer types. Moderate heritability was estimated for total cancer (22%), and most cancer types (Table 1). Prostate cancer, however, showed high heritability (47.3%) and no contribution from shared environment.

Table 1. Summary Results of META Analysis.

Cancer Type	No. of sample groups	No. of twin pairs	Additive Genetic (Heritability), % (95% CI)	Shared Environment, % (95% CI)	Unshared Environment, % (95% CI)	Prevalence, %
Prostate	4	36,247	47.3 (39.2-53.2)	0 (0-0)	52.7 (46.8-58.8)	2.71
Breast	9	68,588	31.9 (22.8-41.2)	20.4 (13.2-27.4)	47.7 (44.3-51.2)	5.00
Cervix	4	50,061	28.5 (9.2-47.9)	16.3 (1.1-31)	55.2 (48.2-62.5)	1.87
Lung	4	125,285	27.6 (13.1-42.2)	18.8 (7.5-29.6)	53.7 (48.4-59.2)	1.33
CRC	3	55,291	25.4 (4.9-45.6)	16.5 (1-31.5)	58.2 (50.7-66.2)	1.69
Stomach	3	55,291	21.0 (0.0-50.0)	19.5 (1-39.1)	59.5 (48.6-71.5)	0.86
Total Cancer	6	81,115	22 (22-22)	14.7 (14.6-19.6)	63.3 (63.3-63.4)	10.41

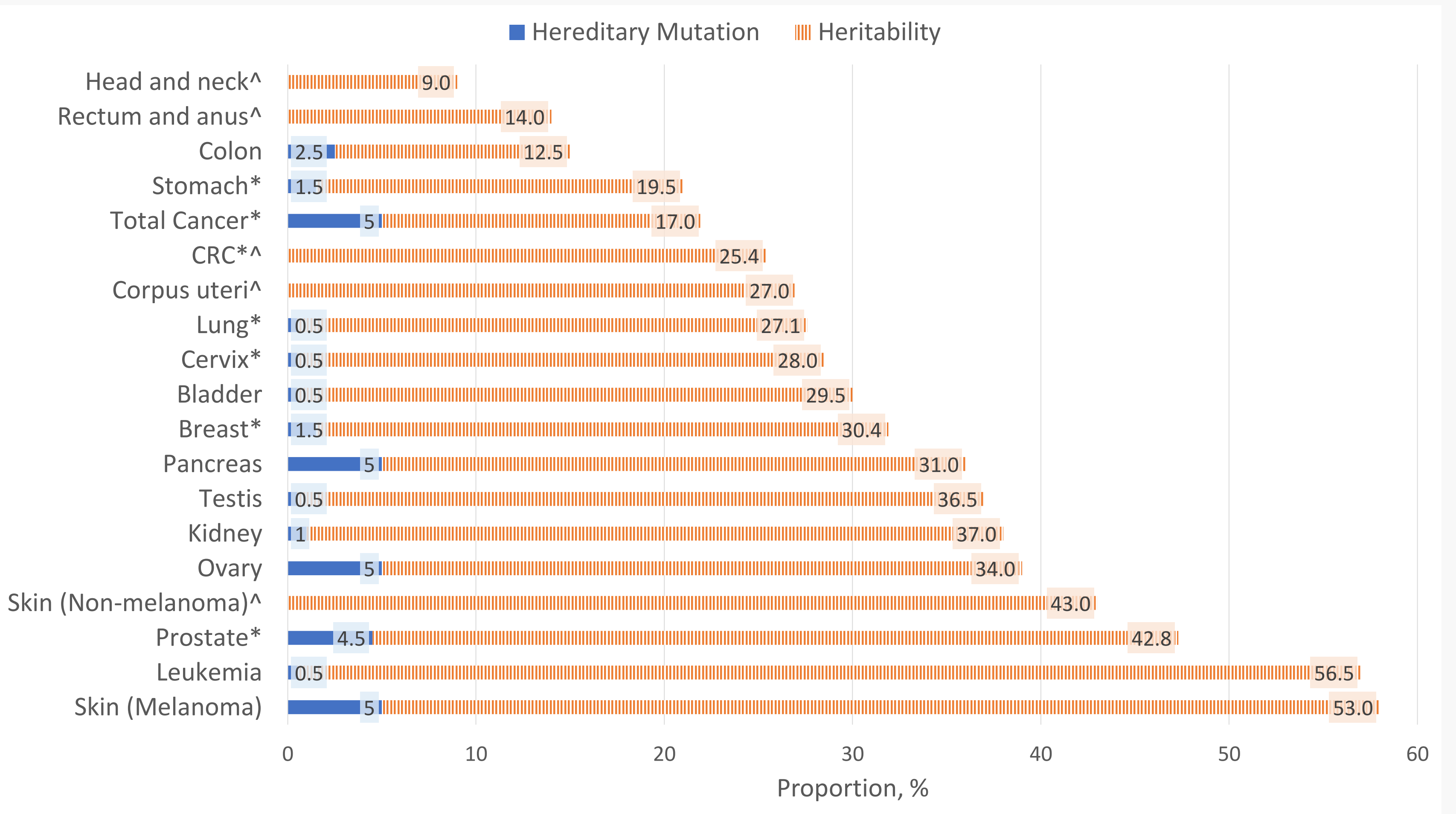
Figure 2. Fraction of Variation Explained by Component and Cancer Type



Notes: \*Cancer types with sufficient data for META analysis, META results were reported. For other cancer types, estimates from the most recent and largest sample were reported.

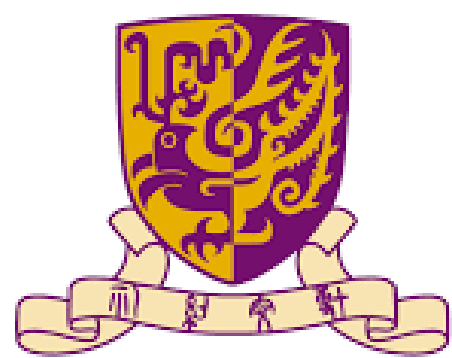
- From twin studies reviewed, unshared environment explained more than 50% of the total variation for over two thirds of all cancer types. It seems that in a way, twin study results support the saying of ‘cancer is mainly due to bad luck’. Nevertheless, there are certain cancers largely due to heritability, such as Melanoma and Leukemia, according to the most recent twin study on largest sample.

Figure 3. Heritability Estimates and Probability attributed to Hereditary Mutation by Cancer Type



Notes: \* Cancer types with sufficient data for META analysis, META results were reported. For other cancer types, estimates from the most recent and largest sample were reported. ^ Cancer types without estimates from Tomasetti et al, 2017.

- A recent study (Tomasetti et al, 2017) on cancer issues suggests that over 80% of cancer risk can be explained by ‘bad luck’, i.e., mutations due to the random mistakes made during normal DNA replication (R). According to their calculation, little of cancer risk was attributable to hereditary (blue bars in Figure 3.).
- Although the concepts of hereditary mutations and heritability are following different definition and the numbers are difficult to compared directly. It is still a natural question when seeing such figure: where does the remaining heritability go? Can inherited genes affect cancer risks in ways other than hereditary mutations? What about interactions between common genetic variants and environment?



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