



# Investigating the Clinical and Genetic Risk of Calcium and Vitamin D on Cancer Development



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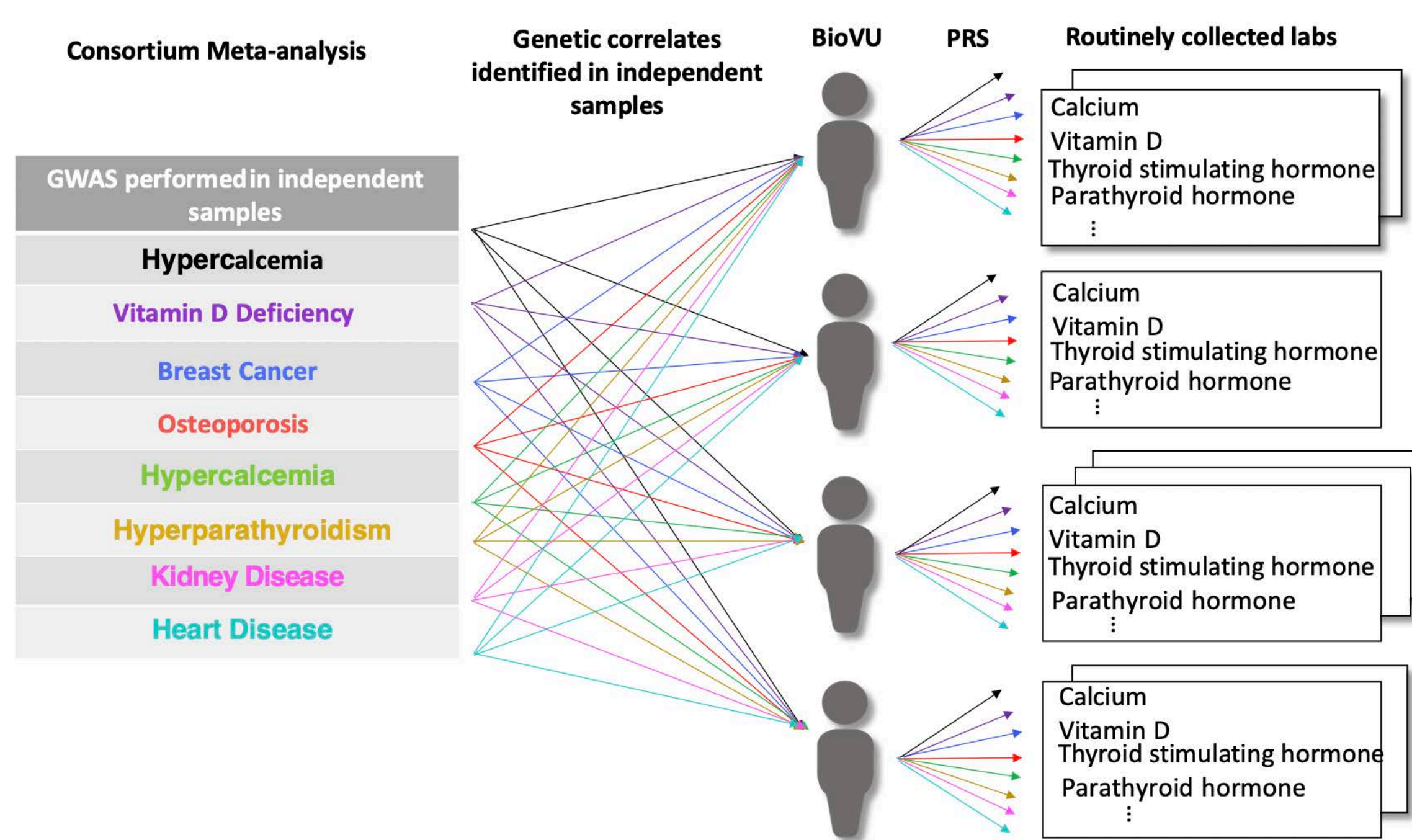
## ABSTRACT

Systemic calcium homeostasis is maintained by the calcium-sensing receptor, which stimulates secretion of parathyroid hormone to promote bone resorption and convert inactive vitamin D to the active form, 1,25(OH) vitamin D, when slight increases in calcium are detected. Unfortunately, calcium signaling dysregulation can lead to the development of many adverse health outcomes such as breast cancer, which disproportionately affects African American women. Although high calcium and vitamin D deficiency have been implicated in cancer progression and metastasis, the associated cancer risk remains poorly understood. In this study, we evaluated the clinical and genetic risk of calcium and vitamin D on cancer development using de-identified electronic health records (EHRs) linked to patient DNA samples in the BioVU biorepository. First, we carried out a series of multivariable regression analyses on clinical cancer diagnoses and laboratory measurements. Using the entire EHR dataset (n = 64,459), we found that high calcium is associated with an increased risk for breast (OR = 1.25, p = 8.98e-22), prostate (OR = 1.26, p = 2.1e-46), and skin (OR = 1.13, p = 1.79e-11) cancers. We also found that high vitamin D levels are significantly associated with skin cancer (OR = 1.23, p = 2.68e-14). With these findings, we sought to understand the association between the genetic liability of these biomarkers, measured by polygenic risk scores (PRS), and cancer risk through a phenotype-wide association study (PheWAS). In our European descent population, we observed that high genetically predicted calcium levels were significantly (p < 0.05) associated with several cancers, with the top association being secondary malignancy of respiratory organs (OR = 1.10, p = 9.43e-04). In our African descent population, we observed that high genetically predicted calcium levels were significantly (p < 0.05) associated with a cluster of breast cancer phenotypes, with the top association being breast cancer in females (OR = 1.20, p = 0.01). Our data shows that although clinical and genetic methods can be used to elucidate cancer etiology, they capture different manifestations of cancer development.

## METHODS

What are the clinical and genetic risk effects of calcium and vitamin D on cancer development?

Schematic of Polygenic Risk Scores (PRS)



Demographics of Genotyped Samples

	European	African
N	53,682	10,777
Mean Age (±SD)	48.74 (22.03)	37.98 (21.57)
Mean BMI (%)	27.75 (7.25)	29.04 (8.65)
Sex (%)		
Female	30,805 (57.4)	6,767 (62.8)
Male	22,877 (42.6)	4,010 (37.2)
Laboratory Values (IQR)		
Calcium (mg/dL)	9.3 (8.95 – 9.5)	9.3 (9.0 – 9.6)
Vitamin D (ng/dL)	30 (24 – 38)	22 (16 – 30)

Table 1. Table showing the descriptive statistics of the European descent and African descent individuals genotyped from the MEGA<sup>EX</sup> platform. IQR = interquartile range

## RESULTS

Figure 1. Forest Plot of Calcium and Cancer

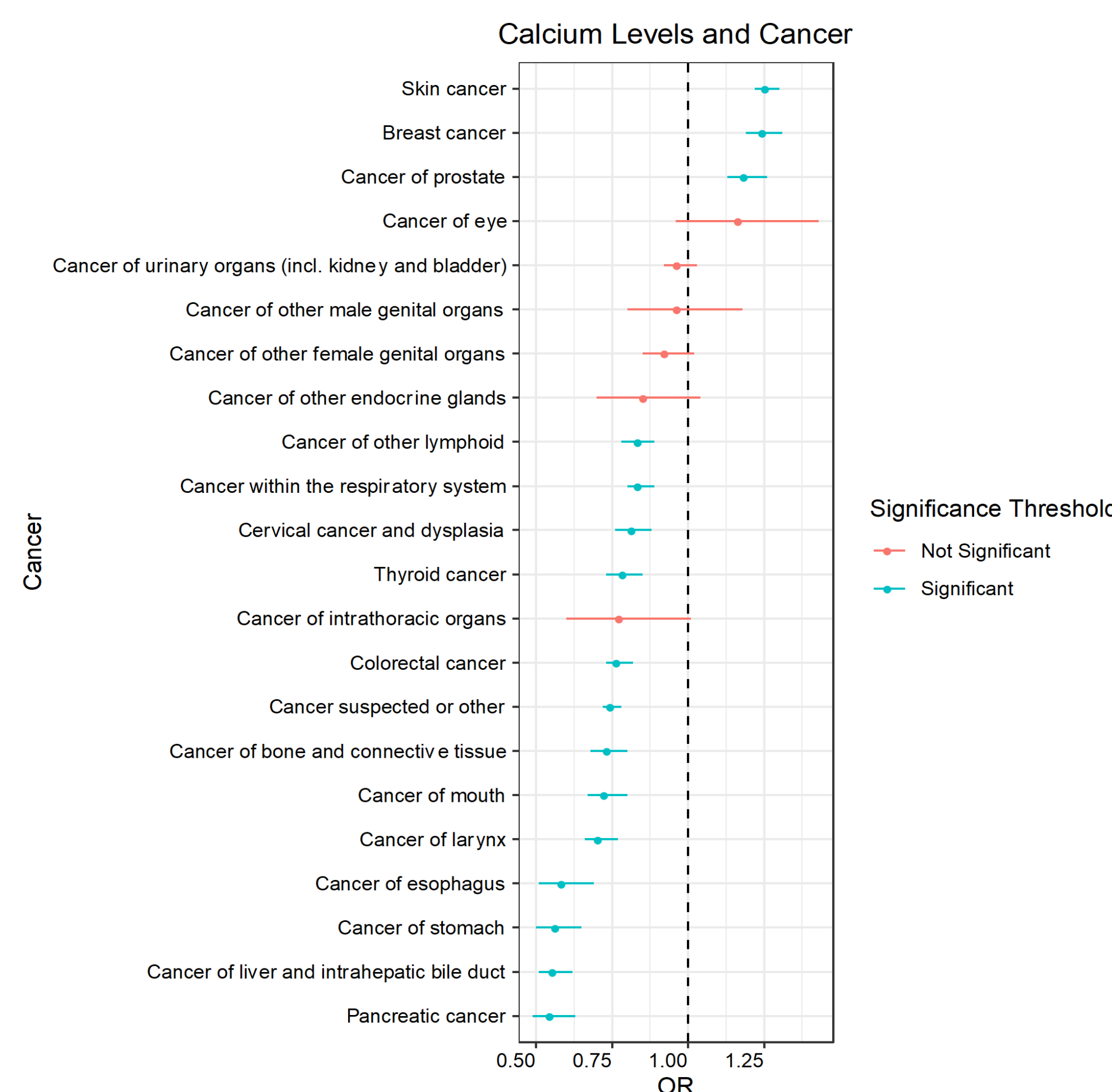


Figure 1. Forest plot of calcium levels and cancer phenotypes. The phenotypes are ordered from highest to lowest odds ratio (OR). The phenotypes that are blue passed Bonferroni correction (p < 5.68e-04). The dash line represents an OR of 1 (no association).

Figure 2. Forest Plot of Vitamin D and Cancer

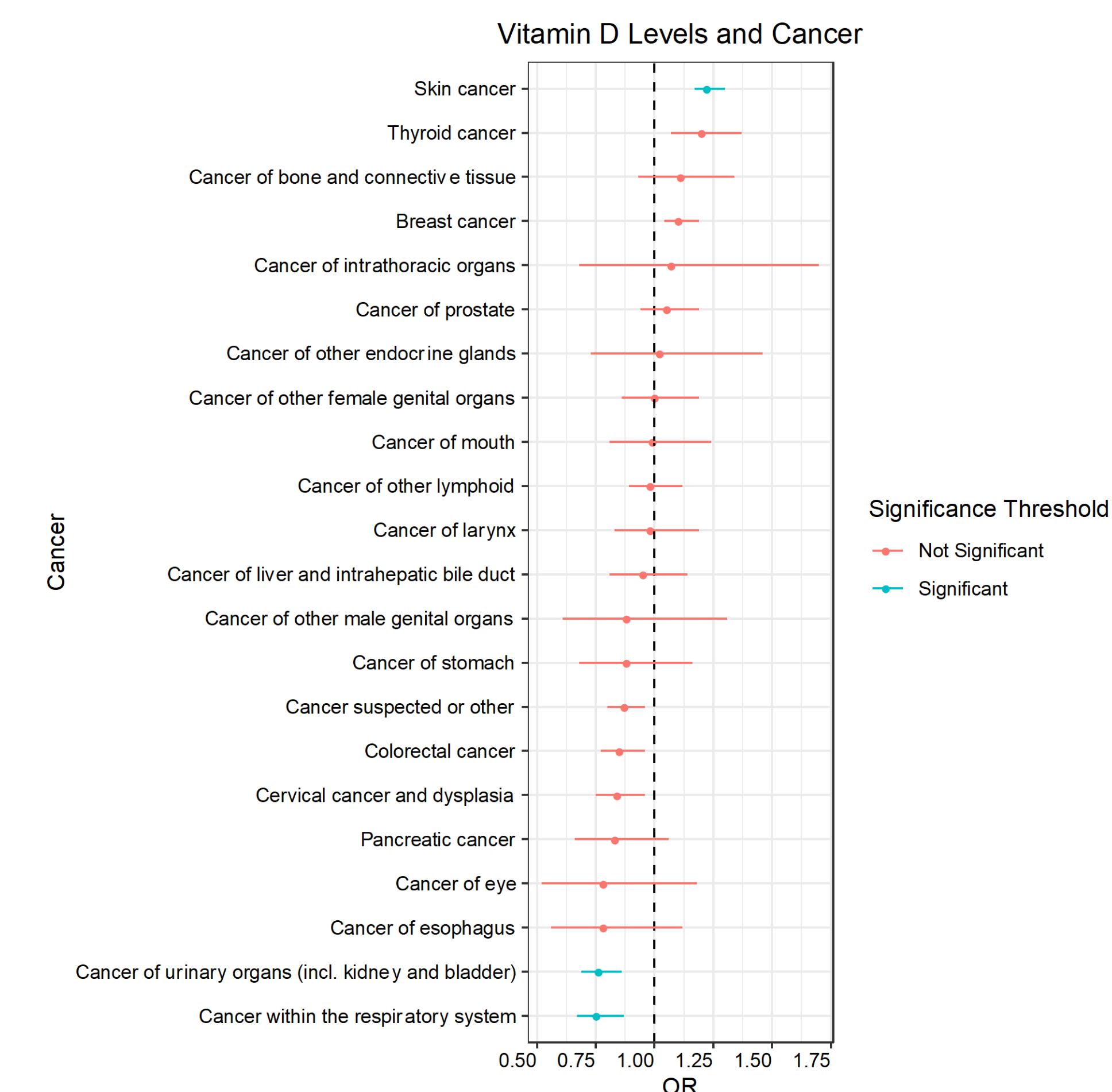


Figure 2. Forest plot of vitamin D levels and cancer phenotypes. The phenotypes are ordered from highest to lowest odds ratio (OR). The phenotypes that are blue passed Bonferroni correction (p < 5.68e-04). The dash line represents an OR of 1 (no association).

Figure 3. European Descent Individuals Calcium PRS-PheWAS

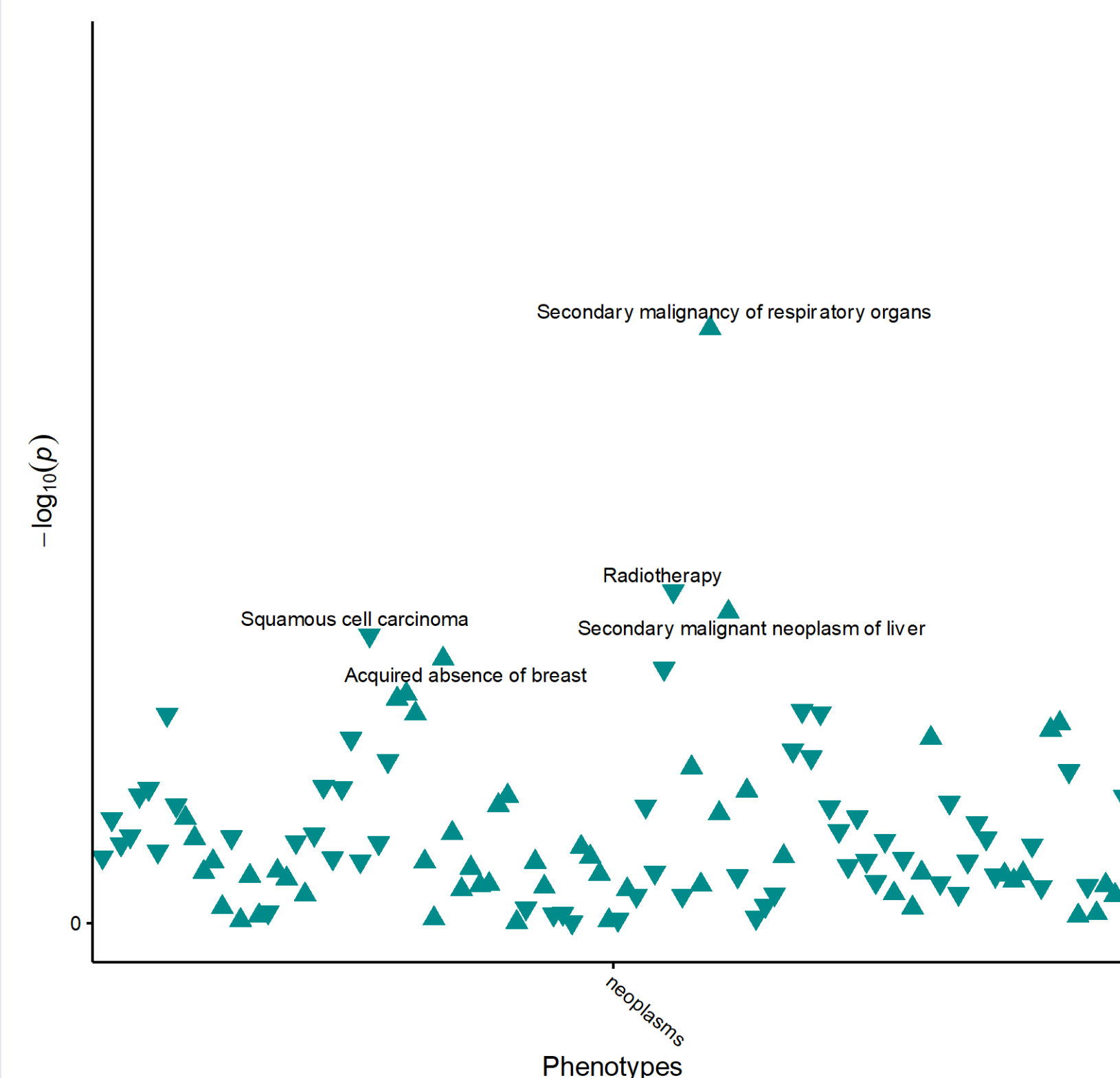


Figure 3. Cancer PheWAS plot of calcium PRS in a European descent sample. The red line is the Bonferroni correction (p < 2.08e-03) and the blue line represents p < 0.05.

Figure 4. African Descent Individuals Vitamin D PRS-PheWAS

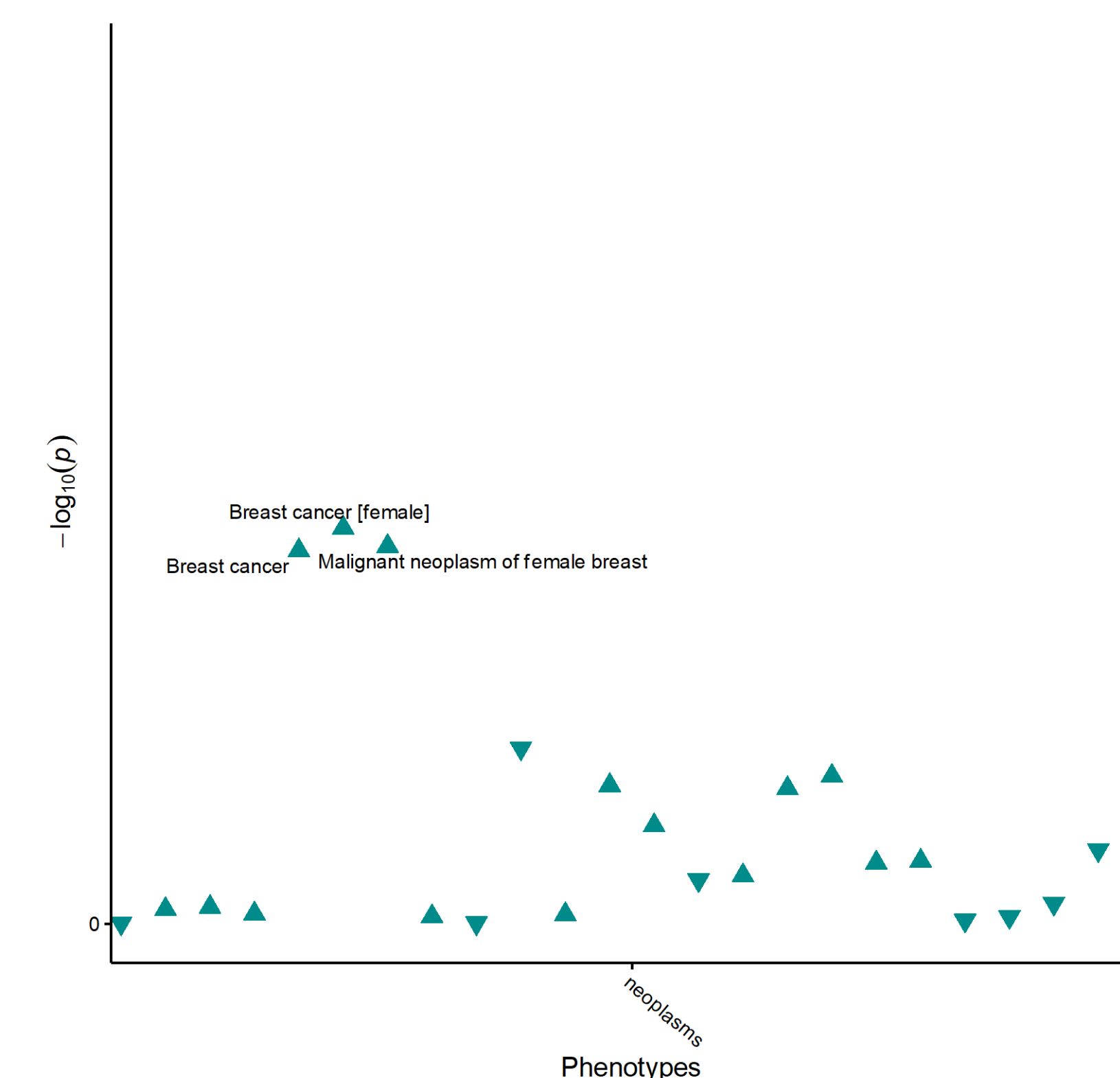


Figure 4. Cancer PheWAS plot of vitamin D PRS in an African descent sample. The red line is the Bonferroni correction (p < 4.46e-04) and the blue line represents p < 0.05.

Neoplasms	Table 2. Laboratory Levels and Cancer				Cases	Controls
	Beta	SE	OR	p		
Calcium						
Skin cancer	0.23	0.02	1.26	2.10E-46	4652	42464
Breast cancer	0.22	0.02	1.25	8.98E-22	2143	46109
Cancer of prostate	0.18	0.03	1.26	.79E-11	1866	45628
Vitamin D						
Skin cancer	0.21	0.03	1.23	2.68E-14	1610	10883

Neoplasms	Table 3. European Descent Individuals Calcium PRS-PheWAS					Cases	Controls
	Beta	SE	OR	p			
Secondary malignancy of respiratory organs							
Radiotherapy	-0.06	0.03	0.94	0.02	1700	40476	
Secondary malignant neoplasm of liver	0.07	0.03	1.08	0.03	955	40476	
Squamous cell carcinoma	-0.08	0.04	0.93	0.03	798	43703	
Acquired absence of breast	0.07	0.04	1.07	0.05	830	45282	

Neoplasms	Table 4. African Descent Individuals Vitamin D PRS-PheWAS					Cases	Controls
	Beta	SE	OR	p			
Breast cancer [female]							
Malignant neoplasm of female breast	0.18	0.07	1.20	0.01	234	9622	
Breast cancer	0.17	0.07	1.19	0.01	244	9622	

## SUMMARY

- High serum calcium levels are significantly associated with an increased risk of skin, breast, and prostate cancer.
- High vitamin D levels are significantly associated with an increased risk of skin cancer.
- Secondary malignancy of respiratory organs is the top association for high genetic risk for calcium in a European descent sample.
- High genetic risk for vitamin D in an African descent sample is significantly associated with breast cancer.

## CONCLUSION

- Our results show that clinical effects of calcium and vitamin D differ from their genetic effects.
- There are possible ancestry-related differences in cancer development based on biomarker genetic susceptibility.
- Experimental follow-up studies are needed to evaluate the underlying mechanisms of these associations.

## ACKNOWLEDGEMENTS

We would like to thank NIH 5T32GM007628 and NIH 1SC1 CA211030 for their support in this project.