Published in final edited form as:

Cancer. 2020 August 15; 126(16): 3617–3619. doi:10.1002/cncr.32915.

Complexities in Estimating the True Risk of Hereditary Leiomyomatosis and Renal Cell Carcinoma and the Development of Kidney Cancer

Mark W. Ball, MD, Christopher J. Rickets, PhD

Urologic Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) is a cancer predisposition syndrome associated with an aggressive variant of renal cell carcinoma (RCC) in some affected individuals. It is caused by pathogenic germline alterations in the gene encoding the Krebs cycle enzyme, fumarate hydratase (*FH*)¹. In recent years, the study of patients affected with this disease has led to improved recognition of the phenotype, early treatment of localized kidney tumors and systemic therapy for treatment of advanced disease². However, many fundamental questions about the disease, including its prevalence, genotype-phenotype correlations, penetrance of its manifestations, and best screening strategies remained to be determined.

The study by Shuch *et al.* in this issue of *Cancer* used large genomic databases along with institutional data to estimate both the frequency of *FH* alterations in the population and the risk of the development of RCC. While the analysis was thorough, it also highlights how imperfect our current tools, including large genomic databases, can be when applied to the study of rare diseases. While the results are intriguing and bolstered by the fact that they are not limited by the biases seen in single institution series, they are subject to some biases on their own.

Incidence data for both a clinical diagnosis of HLRCC and population carrier frequency data is lacking. Incidence data could potentially be derived a few ways. Currently, incidence is inferred from published institutional series. This type of data can be limited in several ways. First, there is no consensus on the clinical definition of HLRCC. While a definitive diagnosis is made based on the presence of a known pathogenic alteration in *FH*, clinical criteria have been proposed. Major criteria indicating a high likelihood of HLRCC include multiple cutaneous leiomyomas with at least one biopsy proven/histologically confirmed, while minor criteria indicating a suspicion for HLRCC include solitary cutaneous leiomyoma and family history of HLRCC, early onset renal tumors of type 2 papillary histology, and/or multiple early onset (<40 years) symptomatic uterine fibroids.³ Clinical criteria become especially relevant when putative novel alterations in *FH* are discovered. Aside from problems with diagnosis, institutional data also relies on publication or case or submission to ClinVar, and it is possible that many centers who manage patients with HLRCC have not published every case they follow. Secondly, there is an inherent referral bias in any

institutional data, reflecting geographic and specialty referral patterns. Finally, relying only on single intuition data excludes the many patients who are likely managed outside of referral centers. Another tool to capture the incidence would be a patient reported registry, similar to the myVHL study ([NCT03749980](#)) for patients with von Hippel-Lindau, but such a registry does not currently exist for HLRCC.

Another option to estimate the incidence of HLRCC is rather than capture cases that meet clinical criteria is to capture the frequency of pathogenic FH alterations in the population. Large genomic registries could be an option to capture the carrier frequency if they are representative of the population at large and not biased either in favor or against capturing patients with HLRCC. It is not clear, however, that such a non-biased registry exists. In the current study, two databases were used: the 1000 Genomes Project (1000GP) and the Exome Aggregation Consortium (ExAc). How representative these databases are for potential patients with HLRCC is unclear. Indeed, the purpose of these databases is different from each other in important ways. 1000GP aimed to gather the germline data for healthy individuals and so would be biased against inclusion of individuals with known diseases. This would only leave HLRCC patients with no clinical phenotype at time of collection and no family history of the disease. Given that there no tier 1 alteration identified in 1000GP, it is likely that, indeed, no patients with HLRCC were included in 1000GP.

In comparison, the ExAc database simply aimed to collate together the germline data collected from a wide range of exome-based projects, many centered around adult diseases. Yet, each project had their own specific aim and so would have collected targeted patients and not wide selection of the general populace. A large number of projects are pooled but that does not necessarily create a reflection of normal population. So dependent upon what projects are included this could be bias both towards or against the inclusion of HLRCC patients. Furthermore, previous studies have demonstrated that most HLRCC manifestations occur at an early age. Cutaneous leiomyomas occur almost in 74-100% of patients with mean age of diagnosis of 24.^{3,4} Similarly, uterine leiomyomas are often early onset, with one series reporting over 30% of women with HLRCC requiring hysterectomy or myomectomy before 30 and 68% by age 40.⁵ Renal tumors can have a variable age of onset, but often occur in young patients with a mean age of 43.^{1,3-7} While demographic data is not available for either 1000GP or ExAc, it likely excludes many patients who would be FH carriers, as most patient have some feature of manifestation of the disease in the first several decades of life. For both databases, it is likely that patients with HLRCC, particularly with lethal RCC would not be included.

There are also potential issues with *in silico* predictive tools for calling Tier 3 alterations. While variants with truncating alterations are likely pathogenic, missense alterations in Tier 3 can be challenging. *In Silico* tools like SIFT and PolyPhen can be problematic for highly conserved genes like *FH*. In the absence of *in vitro* confirmation of loss of protein function, it is distinctly possible that Tier 3 overestimates the frequency of FH carriers.

In the second part of the study, the authors predicted the penetrance of RCC among FH carriers. To comment on the penetrance of RCC among patients with HLRCC, both the numerator of cases and the denominator of carriers needs to be unbiased. A criticism

of existing estimates of the penetrance of kidney cancer among patients with HLRCC is referral bias. For example, for patients referred to dermatology, estimates of the penetrance of cutaneous manifestations may be artificially inflated, while other manifestations may be under representative. For example, in a series surveying dermatologists, the penetrance of cutaneous lesions was 88% while RCC was 1%.⁸ Likewise, among patients referred to urology or medical oncology, estimates of the penetrance of kidney cancer will be inflated compared to other manifestations. In a series reporting only RCC outcomes, the incidence of cutaneous manifestations was lower at 66%.⁹ In the estimates provided in the current manuscript, the denominator of potential carriers is derived from the first part of the study with the intended uncertainty described above. The numerator comes from a few sources including, The Cancer Genome Atlas (TCGA), somatic mutation data from Foundation Medicine and institutional data from Yale and Memorial Sloan Kettering. The TCGA data is problematic as there was a specific attempt to exclude patients with known germline alteration. Patients with *FH* alterations in TCGA could represent either patients with HLRCC that were undiagnosed and thought to be sporadic or they could be sporadic tumors with somatic but not germline alteration in *FH*. This was seen within the TCGA analysis of papillary RCC.¹⁰ Indeed for both TCGA and Foundation cohorts, samples that were only evaluated by somatic mutational analysis should be considered of limited use as any *FH* alteration could be somatic rather than germline and so not representative of a HLRCC patient.

Institutional data on the number of HLRCC patients is inherently subject to referral bias. It is possible that patients with HLRCC are referred to centers with established HLRCC surveillance and treatment programs, and the number of patients with HLRCC seen at a particular center is not reflective of the population at large. At our institution, we follow more than 200 patients with HLRCC, and likewise the proportion of HLRCC patients in our practice does not inform estimates of the population at large.

Undoubtedly, the more we study HLRCC using every tool at our disposal, the more we will learn. With regards to the incidence of HLRCC, it may very well be more common than currently thought, but just as institutional data is limited by biases, the data presented here are not without bias. With this disease, the stakes of underestimating the risk of kidney cancer are high, as it remains one of the most lethal forms of RCC. Additionally, while the window of opportunity to detect and effectively intervene remains unknown in HLRCC, it is likely to be small compared to other forms of RCC due to its early onset and aggressive nature. Early series have demonstrated the high rate of synchronous metastasis at presentation. On the other hand, early detection and surgical intervention of kidney tumors may lead to prolonged survival. Until we have better tools, we continue to advocate for annual screening of all affected individuals with MRI and surgical resection with wide margins of any suspicious renal lesion.

Acknowledgment:

This research was supported by the Intramural Research Program of the National Cancer Institute, NIH

Funding: This research was supported by the Intramural Research Program of the National Cancer Institute, NIH

References

1. Launonen V, Vierimaa O, Kiuru M, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. *Proc Natl Acad Sci U S A*. 2001;98(6):3387–3392. [PubMed: 11248088]
2. Srinivasan R, Su D, Stamatakis L, et al. 5 Mechanism based targeted therapy for hereditary leiomyomatosis and renal cell cancer (HLRCC) and sporadic papillary renal cell carcinoma: interim results from a phase 2 study of bevacizumab and erlotinib. *European Journal of Cancer*. 2014(50):8.
3. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. *Int J Nephrol Renovasc Dis*. 2014;7:253–260. [PubMed: 25018647]
4. Toro JR, Nickerson ML, Wei MH, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. *Am J Hum Genet*. 2003;73(1):95–106. [PubMed: 12772087]
5. Wei MH, Toure O, Glenn GM, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. *J Med Genet*. 2006;43(1):18–27. [PubMed: 15937070]
6. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. *Am J Surg Pathol*. 2007;31(10):1578–1585. [PubMed: 17895761]
7. Gardie B, Remenieras A, Kattygnarath D, et al. Novel FH mutations in families with hereditary leiomyomatosis and renal cell cancer (HLRCC) and patients with isolated type 2 papillary renal cell carcinoma. *J Med Genet*. 2011;48(4):226–234. [PubMed: 21398687]
8. Alam NA, Barclay E, Rowan AJ, et al. Clinical features of multiple cutaneous and uterine leiomyomatosis: an underdiagnosed tumor syndrome. *Arch Dermatol*. 2005;141(2):199–206. [PubMed: 15724016]
9. Grubb RL 3rd, Franks ME, Toro J, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. *J Urol*. 2007;177(6):2074–2079; discussion 2079–2080. [PubMed: 17509289]
10. Cancer Genome Atlas Research N, Linehan WM, Spellman PT, et al. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N Engl J Med*. 2016;374(2):135–145. [PubMed: 26536169]