Is the Mutational Landscape of Hepatocellular Adenoma Distinct in the Setting of Oral Contraceptive Use?

Caitlyn J. Smith BS, Keela R. Scott MD, Alex Hinken BS, Deepthi S. Rao MD, MS, FCAP

Department of Pathology & Anatomical Sciences, University of Missouri, Columbia, MO 65212, USA

(The authors have no conflicts of interest as it relates to the content of this abstract)

Introduction

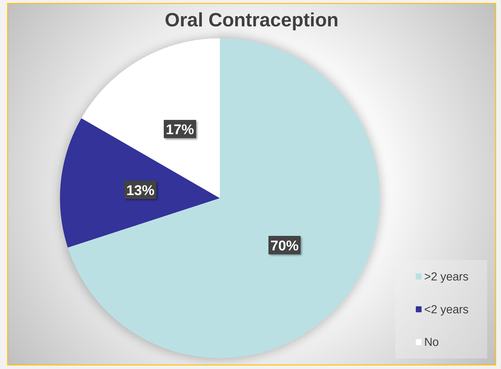
- Hepatocellular adenomas (HCA) are benign tumors with two major complications: bleeding and malignant transformation.
- Solitary or multiple hepatocellular development in the normal liver of women of childbearing age exposed to oral contraceptives still represents the most frequent clinical context.
- However, the impact of mutation frequency on HCA and its correlation to oral contraceptive use is largely unknown.

Objective

This study investigates the multifactorial role of oral contraceptive use and its effect on mutation frequency, mutation count, and nodule size in patients with HCA.

Methods

- Using the cBioPortal platform and systematic bioinformatical analysis of the Cancer Genome Atlas (INSERM) Cancer Cell 2014 data for hepatocellular adenoma, 30 HCA patients were included in this study.
- Of which 21 patients had used oral contraception for >2 years, 4 patients <2 years, and 5 patients had no reported history of oral contraceptive use.



Results & Figures

Figure A. HCA is composed of mature-appearing hepatocytes arranged in thin, 1- to 2-cell-thick plates. Unpaired arteries (black solid arrow) and absence of portal tracts help in distinction from normal liver.

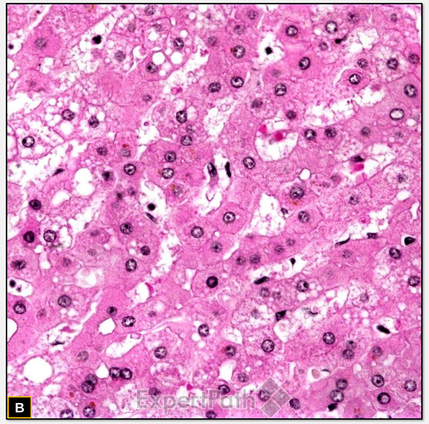


Figure B. High-power view of the neoplastic hepatocytes in HCA illustrates their uniformity and low nuclear:cytoplasmic ratio.

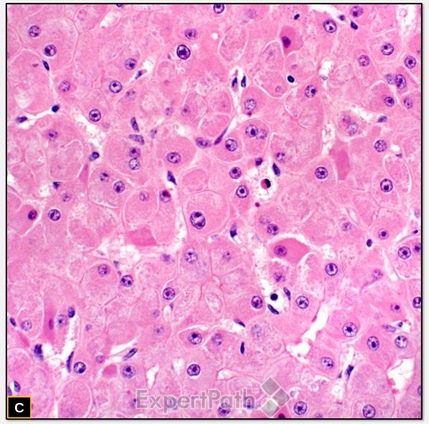


Figure C. The neoplastic hepatocytes show nuclear enlargement and uniform prominent nucleoli in this hepatocellular tumor with β-catenin activation.

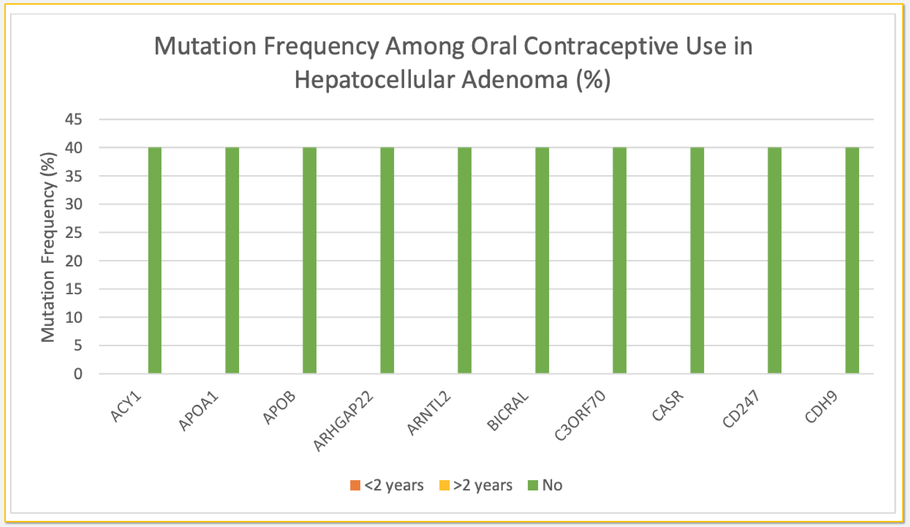


Figure 3. Graphical representation of mutational frequency among oral contraceptive use in hepatocellular adenoma

Discussion

- The mutational landscape of the lack of oral contraceptive use associated with HCA was distinct with statistically significant alterations in ACY1, APOA1, APOB, ARHGAP22, ARNTL2, BICRAL, C3ORF70, CASR, CD247, CDH9 mutation frequency (See Figure).
- Further, the mutation count was statistically significant as patients with no history of HCA had a median mutation count of 19.
- Patients with oral contraceptive use >2 years had a median mutation count of 11, whereas patients with oral contraceptive use <2 years had a 6, respectively (p-value = 0.03).
- Additionally, the nodule size (mm) in patients with HCA was statistically significant as patients with no history of oral contraceptive use and patients with a history of oral contraceptive use >2 years had a median nodule size of 70 mm, whereas patients with a history of oral contraceptive use <2 years had a median nodule size of 37.5 mm (p-value = 0.03).

Conclusion

The findings in this study highlight the complex multifactorial role of oral contraceptive use in HCA.

Further studies are essential for understanding the molecular and pathophysiologic impact of oral contraceptive use on functions of critical genes that exert carcinogenic potential.

References

1. Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenoma: Classification, variants and clinical relevance. Semin Diagn Pathol. 2017 Mar;34(2):112-125. doi: 10.1053/j.semdp.2016.12.007. Epub 2016 Dec 20. PMID: 28131467.
2. Kakar, Sanjay, and Matthew M Yeh. "Hepatocellular Adenoma." ExpertPath, Elsevier, https://app.expertpath.com/document/hepatocellular-adenoma/ace456f1-313a-473e-8afc-ef19e1730791. Accessed 18 Aug. 2022.
3. Bioulac-Sage P, Sempoux C, Balabaud C. Hepatocellular adenoma: Classification, variants and clinical relevance. Semin Diagn Pathol. 2017 Mar;34(2):112-125. doi: 10.1053/j.semdp.2016.12.007. Epub 2016 Dec 20. PMID: 28131467.
4. Aamann L, Schultz N, Fallentin E, Hamilton-Dutoit S, Vogel I, Grønbæk H. Leveradenomer – ny klassifikation og anbefalinger [Hepatocellular adenoma - new classification and recommendations]. Ugeskr Laeger. 2015 Mar 16;177(12):V07140397. Danish. PMID: 25786843.
5. Bioulac-Sage P, Gouw ASH, Balabaud C, Sempoux C. Hepatocellular adenoma: what we know, what we do not know, and why it matters. Histopathology. 2022 May;80(6):878-897. doi: 10.1111/his.14605. Epub 2022 Mar 15. PMID: 34856012.

Acknowledgements

The authors would like to thank the department of Pathology & Anatomical Sciences for the opportunity.