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A comprehensive study of HMG-CoA reductase in Uterine cancer with an *in silico* perspective

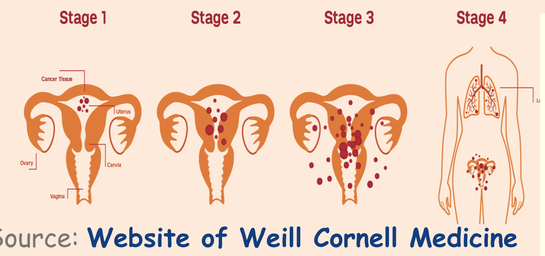
Priti Chatterjee*

***Assistant Professor, Department of Zoology, Krishnagar Govt. College, Krishnanagar, Nadia, West Bengal, PIN- 741101, India.**

e-mail: pritichatterz@gmail.com

INTRODUCTION & OBJECTIVE

Uterine Cancer and its types



Source: Website of Weill Cornell Medicine

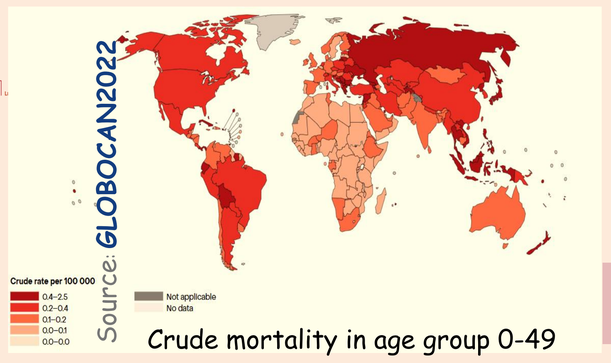
Uterine Corpus Endometrial Carcinoma (UCEC):

- **Definition:** UCEC is a cancer that originates in the lining of the uterus (endometrium).
- **Prevalence:** It is the most common type of uterine cancer.
- **Genetic Changes:** UCEC often exhibits genetic alterations, including mutations in genes like TP53, PTEN, PIK3CA, and PPP2R1A.

Uterine Carcinosarcoma (UCS):

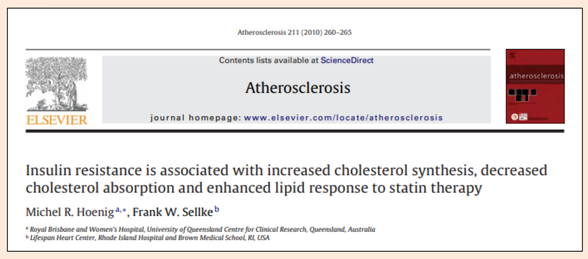
- **Definition:** UCS is characterized by both cancerous epithelial cells (carcinoma) and muscle cells (sarcoma).
- **Prevalence:** UCS is found in less than 5% of uterine cancers.
- **Genetic Changes:** UCS shares some genetic alterations with UCEC, including mutations in TP53 and PTEN.

Uterine Cancer and the global scenario



Crude mortality in age group 0-49

Background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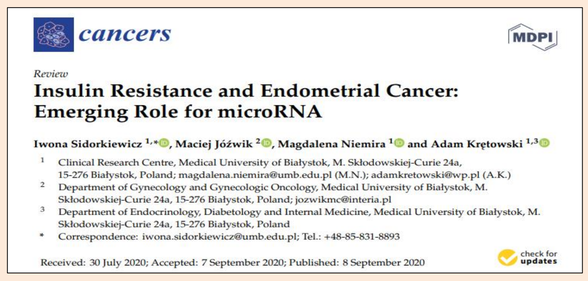
Insulin resistance is associated with increased cholesterol synthesis, decreased cholesterol absorption and enhanced lipid response to statin therapy

Michel R. Hoenig[a,*], Frank W. Sellke[b]

[a] Royal Brisbane and Women's Hospital, University of Queensland Centre for Clinical Research, Queensland, Australia
[b] Lifespan Heart Center, Rhode Island Hospital and Brown Medical School, RI, USA


cancers

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Review

Insulin Resistance and Endometrial Cancer: Emerging Role for microRNA

Iwona Sidorkiewicz [1,*], Maciej Jóźwik [2], Magdalena Niemira [1] and Adam Krętowski [1,3]

1 Clinical Research Centre, Medical University of Białystok, M. Skłodowskiej-Curie 24a, 15-276 Białystok, Poland; magdalena.niemira@umb.edu.pl (M.N.); adamkretowski@wp.pl (A.K.)
2 Department of Gynecology and Gynecologic Oncology, Medical University of Białystok, M. Skłodowskiej-Curie 24a, 15-276 Białystok, Poland; jozwikmc@interia.pl
3 Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Białystok, M. Skłodowskiej-Curie 24a, 15-276 Białystok, Poland
* Correspondence: iwona.sidorkiewicz@umb.edu.pl; Tel.: +48-85-831-8893

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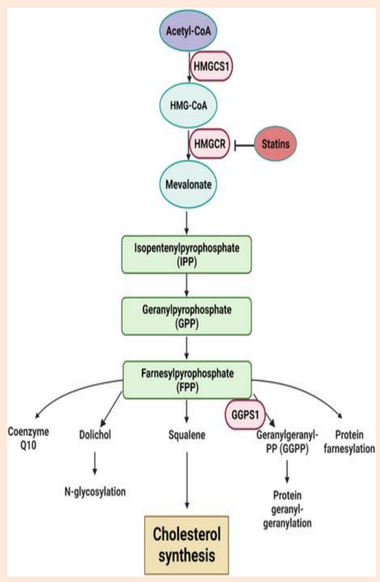
check for updates

Can fertility preservation be an option????

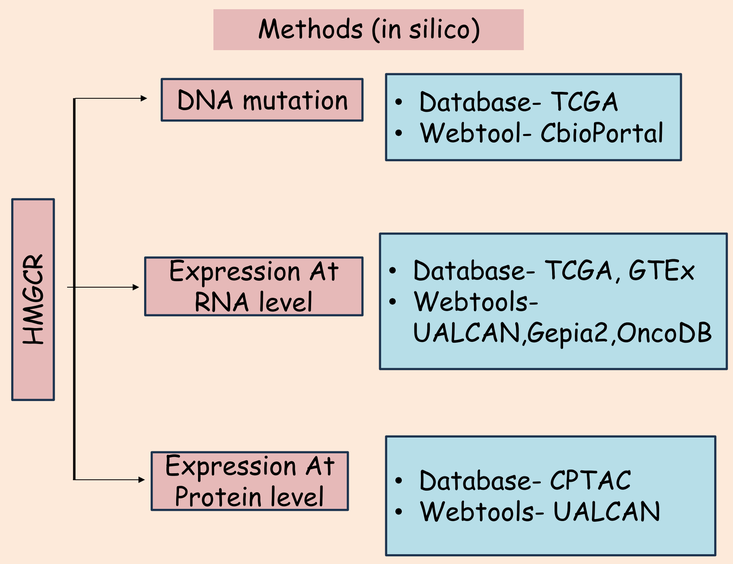


Source: https://doi.org/10.1111/febs.17406

Objective

To understand the clinical implications of HMG-CoA reductase in both subtypes of uterine cancer.

METHODS



GEPIA2 Gene Expression Profiling Interactive Analysis — https://gepia2.cancer-pku.cn/

OncoDB — https://oncodb.org/

cBioPortal FOR CANCER GENOMICS — https://www.cbioportal.org/

UALCAN Analyze, Integrate, Discover — https://ualcan.path.uab.edu/

RESULTS AND DISCUSSION

Figure 1

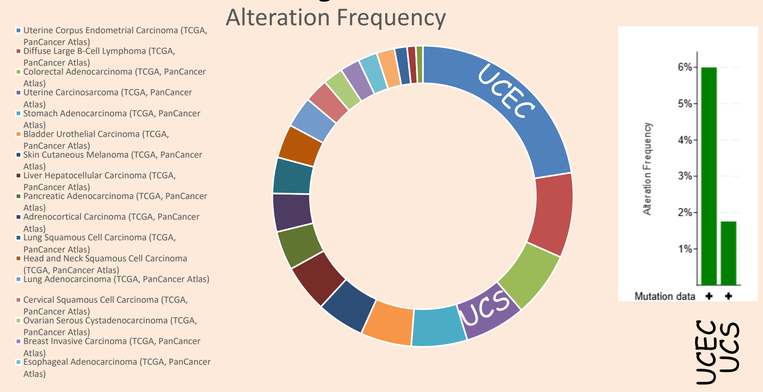


Figure 1: TCGA data accessed through cBioPortal showing higher percentage of mutational anomalies in the UCEC (6%) patients compared to UCS(1.75%).

Figure 2

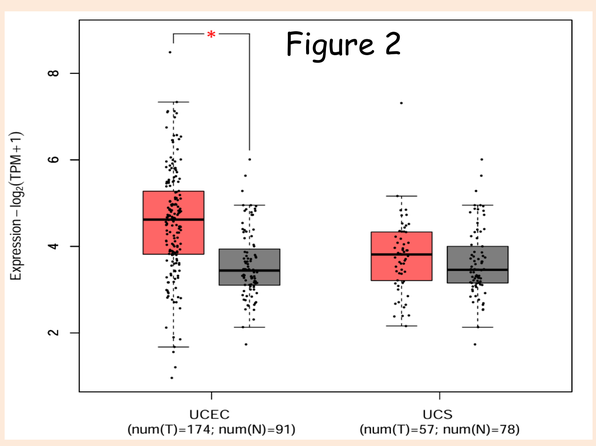
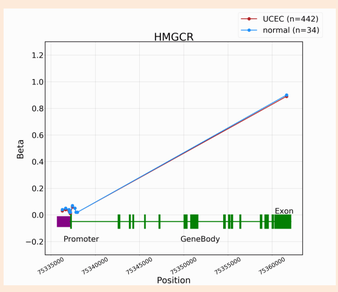


Figure 2: HMGCR is significantly upregulated in UCEC patients at mRNA level (GEPIA2). TCGA tumor samples in red (UCEC N= 174, UCS N= 57), TCGA + GTEx normal samples in grey (UCEC control =91; UCS control =78)

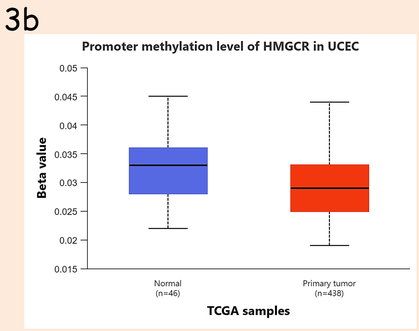
Figure 3a



Significant probe highlighted (p<0.05)

Gene	Probe	Chr	Position	Average of Cancer Sample	Average of Normal Sample	p-value
HMGCR	cg11003009	chr5	75336287	0.03	0.04	5.0e-04
HMGCR	cg07025548	chr5	75336652	0.04	0.05	1.5e-01
HMGCR	cg24854943	chr5	75337033	0.03	0.04	4.8e-02
HMGCR	cg05910138	chr5	75337097	0.02	0.03	2.1e-01
HMGCR	cg02162412	chr5	75337101	0.03	0.03	7.4e-02
HMGCR	cg18880544	chr5	75337110	0.03	0.03	8.7e-01
HMGCR	cg06434480	chr5	75337115	0.02	0.02	8.2e-01
HMGCR	cg10552847	chr5	75337141	0.02	0.02	6.8e-01
HMGCR	cg26685658	chr5	75337187	0.02	0.02	4.3e-01
HMGCR	cg09026481	chr5	75337197	0.01	0.02	2.7e-01
HMGCR	cg07732421	chr5	75337428	0.06	0.07	4.9e-02
HMGCR	cg00360362	chr5	75337702	0.05	0.05	3.4e-01
HMGCR	cg26399773	chr5	75337830	0.02	0.02	2.5e-01
HMGCR	cg11213898	chr5	75337995	0.02	0.02	8.8e-02
HMGCR	cg26510404	chr5	75361623	0.89	0.90	6.1e-01

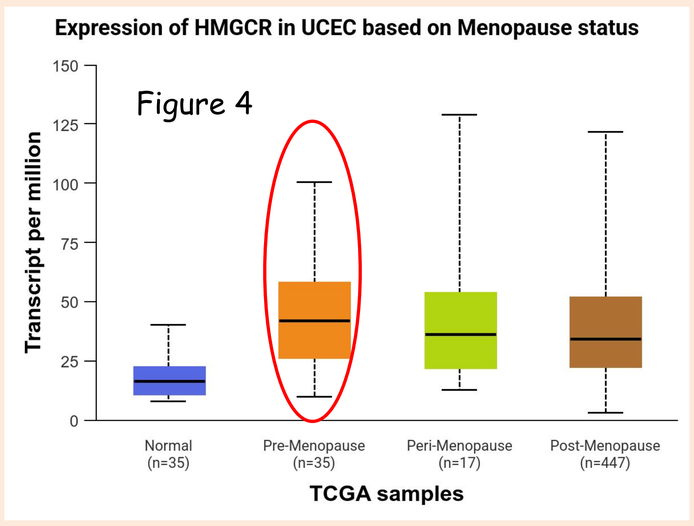
Figure 3b



Comparison	Statistical significance
Normal-vs-Primary	2.802600E-04

Figure 3: Promoter methylation of HMGCR is relatively lower in UCEC patients as derived from a) OncoDB and b) UALCAN (TCGA samples: Normal in blue ,N=46; Primary Tumor in red, N= 438.

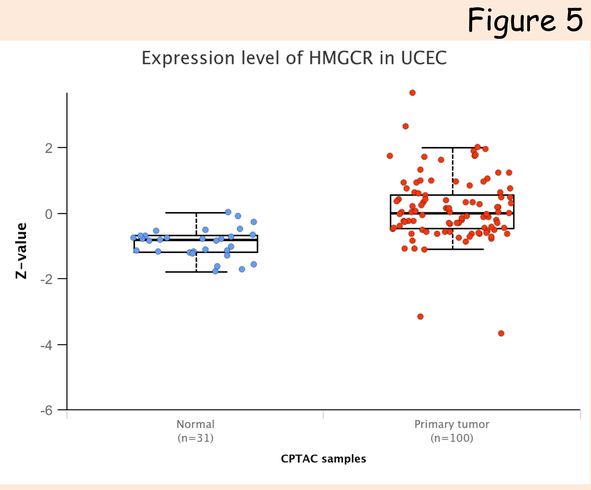
Figure 4



Comparison	Statistical significance
Normal-vs-Pre-Menopause	2.3600999998763E-07
Normal-vs-Peri-Menopause	1.480070E-02
Normal-vs-Post-Menopause	1.62447832963153E-12
Pre-Menopause-vs-Peri-Menopause	4.946600E-01
Pre-Menopause-vs-Post-Menopause	3.612800E-01
Peri-Menopause-vs-Post-Menopause	6.511600E-01

Figure 4: HMGCR is significantly upregulated in UCEC patients in pre-menopause stage.

Figure 5



Comparison	Statistical significance
Normal-vs-Primary	6.30388516086518E-13

Figure 5: HMGCR is significantly upregulated in UCEC patients at protein level (UALCAN) CPTAC samples: Normal (blue) N= 31; Primary Tumor (red) N= 100

SUMMARY

- HMGCR shows higher percentage of mutational anomalies in UCEC patients compared to UCS patients.
- HMG CoA Reductase is increased at transcript levels in the UCEC samples but not in UCS tissues.
- The promoter region of HMG CoA Reductase gene has less methylation marks compared to normal samples indicating the transcriptional hyperactivity of the gene in UCEC.
- Therefore, statins might be an alternative choice of medication to harness endometrial cancer and is yet to be confirmed through *in vitro* studies.

FUTURE WORK-PLAN

- To identify the mutations of HMGCR and predict their impact on the protein structures and functions.
- To predict the high-concern mutations and their effect on the binding of statins through molecular docking. (comparing with Wildtype)
- This might help in predicting if the particular statin could be effective in pre-menopausal women.

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