PS2-08-29: Plasma hepcidin as a prognostic biomarker in early breast cancer: a pooled cohort analysis

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Background

- A high proportion of patients with early-stage breast cancer (BC) will experience disease recurrence during their life-time; obesity is associated with an ~30% increased risk of recurrence[1].
- Chronic inflammation and metabolic dysfunction are thought to contribute to the adverse prognosis associated with obesity[4,6].
- Elevated levels of hepcidin, an inflammatory marker and a peptide hormone that regulates iron, has been associated with higher risk of distant BC recurrence and death among obese women[2].

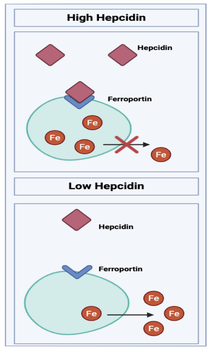
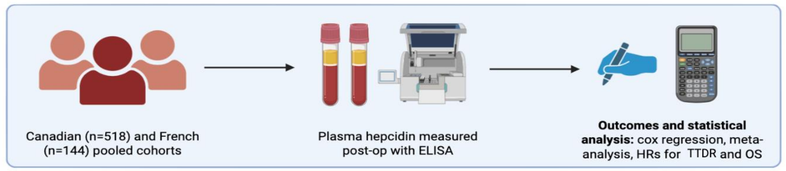


Fig. 1. Hepcidin binds to the iron exporter ferroportin, triggering its internalization & degradation. This increases intracellular iron stores[3,5].

Objective: To assess whether elevated plasma hepcidin levels, identified after definitive surgery and prior to adjuvant systemic therapy for early-stage BC, are associated with shorter time to distant recurrence (TTDR) and overall survival (OS) among obese women.

Methods

- We performed a pooled analysis of two prospective cohorts of women with early-stage BC (Canadian n=518; French n=144).
- Plasma was collected postoperatively and prior to initiation of adjuvant systemic therapy.
- TTDR was defined as the time from BC diagnosis to first distant recurrence, censored at last follow up, non-BC event, or death. OS was defined as the time from BC diagnosis to death from any cause.
- Cox regression models were fitted to each data set, treating hepcidin as a continuous variable. and with a hepcidin-by-body mass index (BMI: kg/m^2) interaction (BMI dichotomized at 30).
- Cohort-specific 'beta' coefficients and standard errors from each survival model were combined meta-analytically using a random effect model, with results presented as hazard ratios (HRs) and 95% confidence intervals (CIs).



Results

- In total, 662 patients were included.
- The median age was 48.6 years across both cohorts.
- Most patients (88.9%) had T1 or T2 tumors; approximately two-thirds had lymph node-negative disease (69.9% Canadian cohort; 52.8% French cohort).
- In total, 16.4% and 16.0% of patients in the Canadian and French cohorts were obese (BMI≥30).
- In a pooled analysis, **elevated plasma hepcidin was significantly associated with shorter TTDR (adjusted HR 2.23; 95%CI 1.23-4.07) and shorter OS (adjusted HR 1.87; 95%CI 1.03-3.39) among obese women**.
- Conversely, no statistically significant associations were identified among non-obese women for either TTDR or OS.

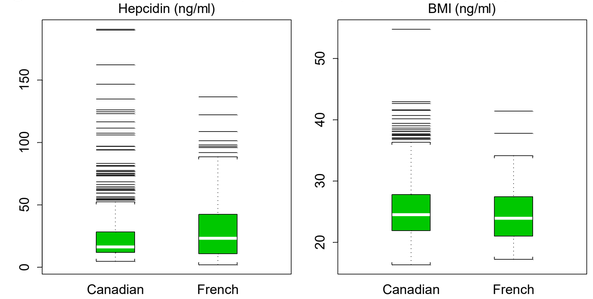
Table 1. Unadjusted and adjusted Cox models showing overall hazard ratios for hepcidin (75th percentile versus 25th percentile[1]), for the outcomes TTDR and OS

			Unadjusted		Adjusted*[2]	
Outcome	Cohort	BMI Group	HR (95% CI)	Interaction p-value	HR (95% CI)	Interaction p-value
Time to Distant Recurrence	Canadian	<30	0.78 (0.55-1.10)	0.010	0.94 (0.67-1.33)	0.024
		≥30	1.96 (1.07-3.59)		2.09 (1.12-3.88)	
	French	<30	0.67 (0.36-1.25)	0.247	0.61 (0.31-1.22)	0.068
		≥30	1.99 (0.35-11.44)		5.55 (0.58-53.38)	
	Meta-analysis	<30	0.75 (0.56-1.02)		0.84 (0.58-1.22)	
		≥30	1.96 (1.11-3.48)		2.23 (1.23-4.07)	
Overall Survival	Canadian	<30	0.98 (0.69-1.38)	0.030	1.04 (0.73-1.48)	0.113
		≥30	2.07 (1.15-3.74)		1.80 (0.98-3.29)	
	French	<30	1.01 (0.50-2.06)	0.555	0.80 (0.36-1.80)	0.249
		≥30	2.22 (0.18-27.55)		6.46 (0.21-203)	
	Meta-analysis	<30	0.98 (0.72-1.34)		1.00 (0.72-1.38)	
		≥30	2.08 (1.17-3.70)		1.87 (1.03-3.39)	

[1]25th and 75th percentiles of hepcidin were 11.6ng/ml and 31.3ng/ml. [2]Adjusted for variables age, T-stage, tumor grade, nodal status, and hormone receptor status

Results

Figure 2. Distributions of plasma hepcidin and BMI by cohort.



Conclusions

Obesity is associated with a higher risk of recurrence and death among women with early-stage BC.

Higher plasma hepcidin levels are independently associated with a significantly shorter TTDR and OS among obese women with early-stage BC, but not among their non-obese counterparts.

Biological mechanisms underlying this finding warrant further study.

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