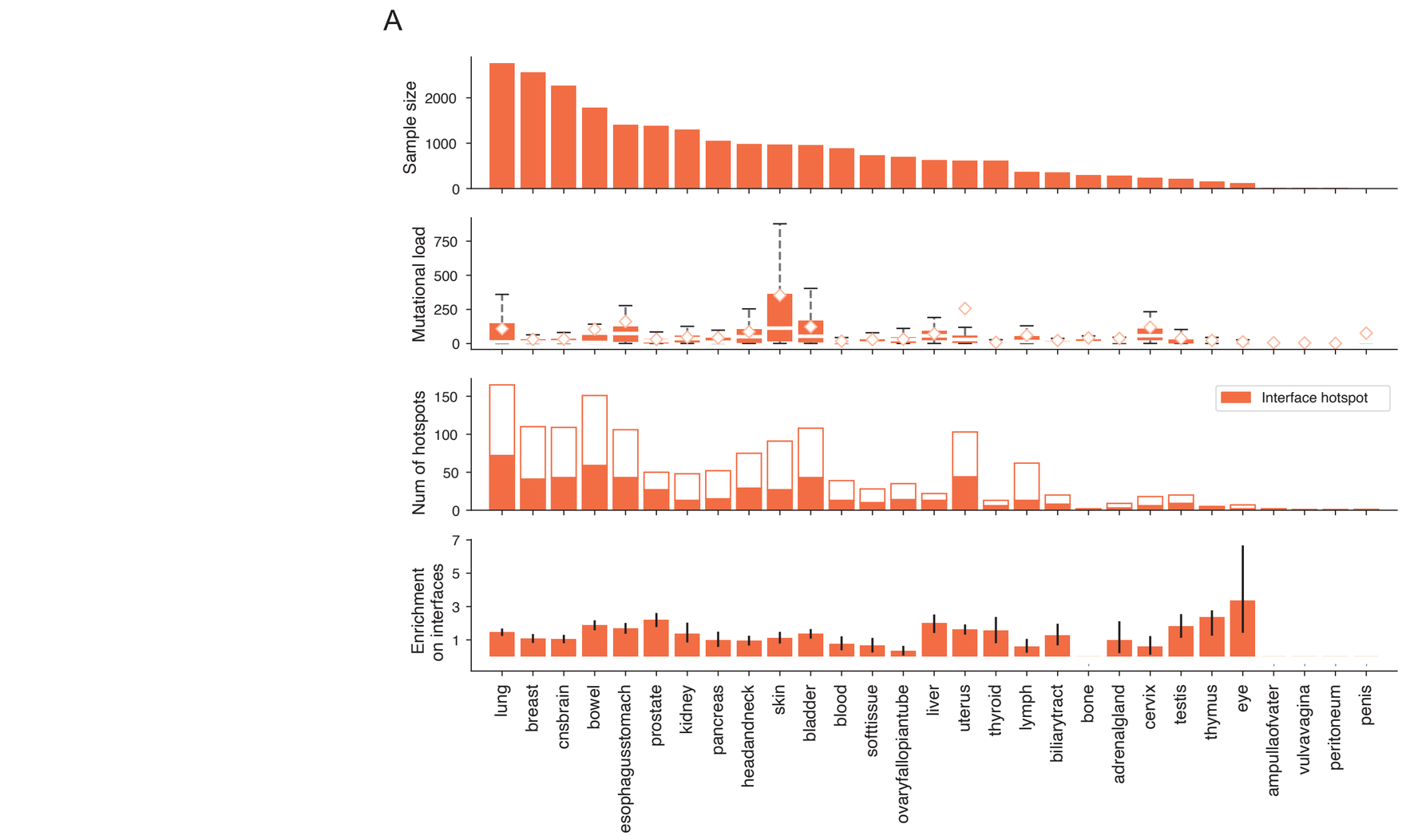

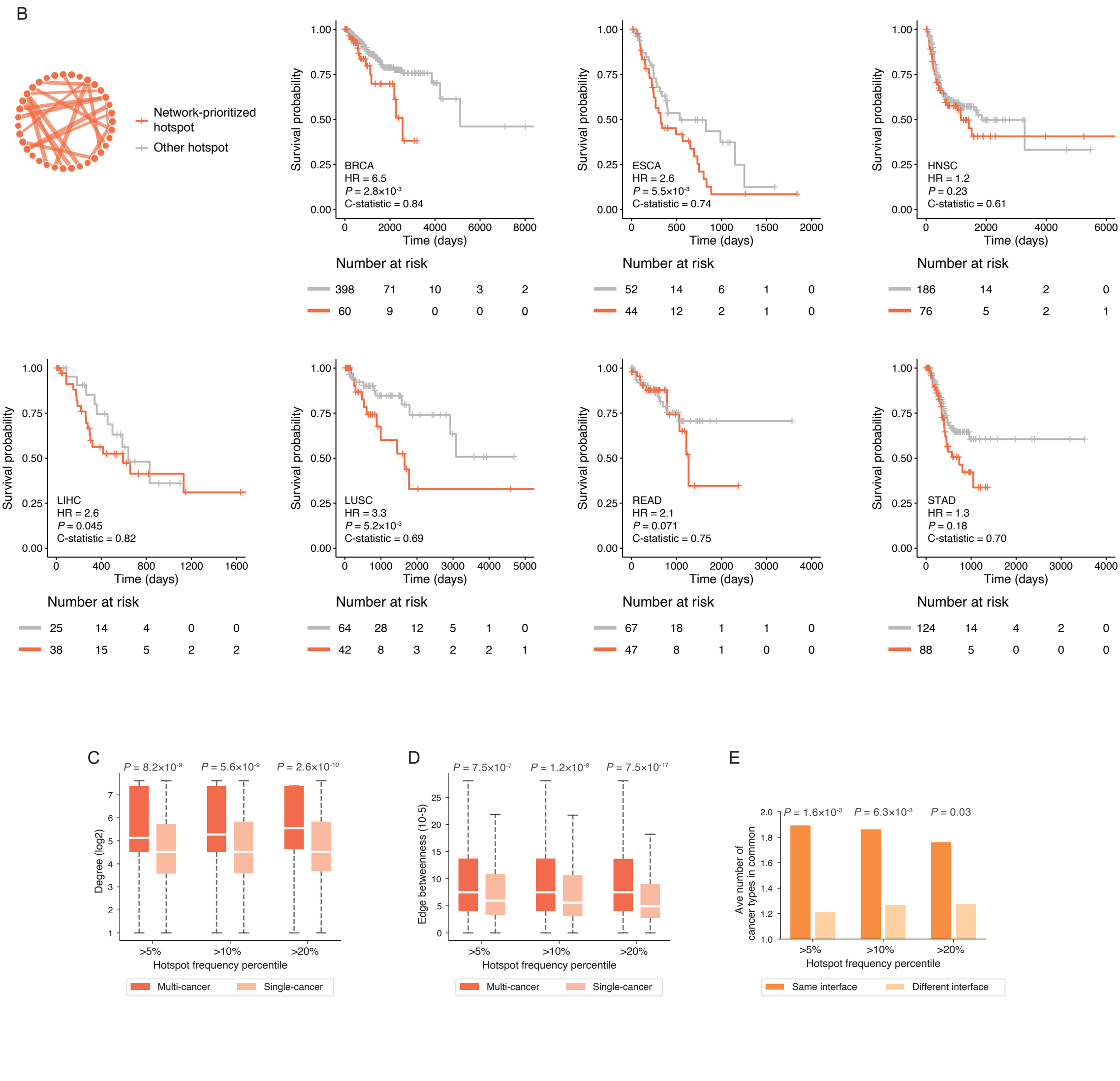

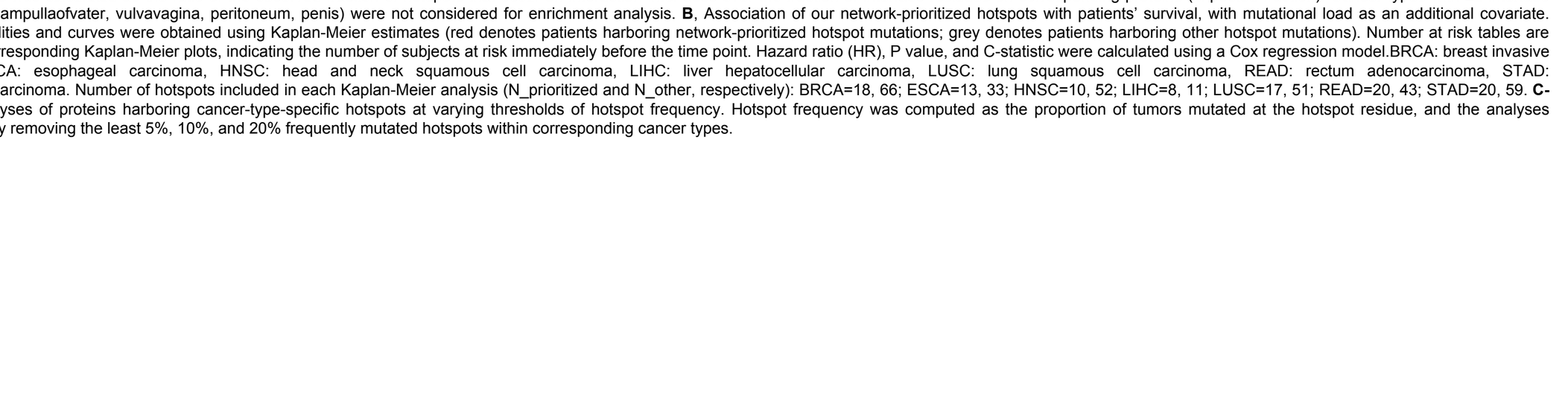

Supplementary Fig. 10: Sample size, mutational load, and hotspot frequency in cancer-type-specific hotspot analysis. **A**, Summary of sample sizes, mutational loads, and numbers of hotspots detected in specific cancer types against the enrichment of cancer-type-specific hotspots on protein interfaces. Cancer types were ordered by their sample sizes as reported in the original hotspot detection analysis. Mutational load was calculated as the total number of non-synonymous mutations in each cancer patient and then aggregated across different cancer types. Diamond indicates the mean value of mutational load in the corresponding cancer type. Enrichment of cancer-type-specific hotspots on protein interfaces was calculated as the ratio of the observed fraction of hotspots that occur on interaction interfaces over the fraction of interface residues on corresponding proteins (expected fraction). Cancer types with ≤2 interface hotspots (bone, ampullaofvater, vulvavagina, peritoneum, penis) were not considered for enrichment analysis. **B**, Association of our network-prioritized hotspots with patients' survival, with mutational load as an additional covariate. Survival probabilities and curves were obtained using Kaplan-Meier estimates (red denotes patients harboring network-prioritized hotspot mutations; grey denotes patients harboring other hotspot mutations). Number at risk tables are shown under corresponding Kaplan-Meier plots, indicating the number of subjects at risk immediately before the time point. Hazard ratio (HR), P value, and C-statistic were calculated using a Cox regression model.BRCA: breast invasive carcinoma, ESCA: esophageal carcinoma, HNSC: head and neck squamous cell carcinoma, LIHC: liver hepatocellular carcinoma, LUSC: lung squamous cell carcinoma, READ: rectum adenocarcinoma, STAD: stomach adenocarcinoma. Number of hotspots included in each Kaplan-Meier analysis (N_prioritized and N_other, respectively): BRCA=18, 66; ESCA=13, 33; HNSC=10, 52; LIHC=8, 11; LUSC=17, 51; READ=20, 43; STAD=20, 59. **C-E**, Network analyses of proteins harboring cancer-type-specific hotspots at varying thresholds of hotspot frequency. Hotspot frequency was computed as the proportion of tumors mutated at the hotspot residue, and the analyses were repeated by removing the least 5%, 10%, and 20% frequently mutated hotspots within corresponding cancer types.