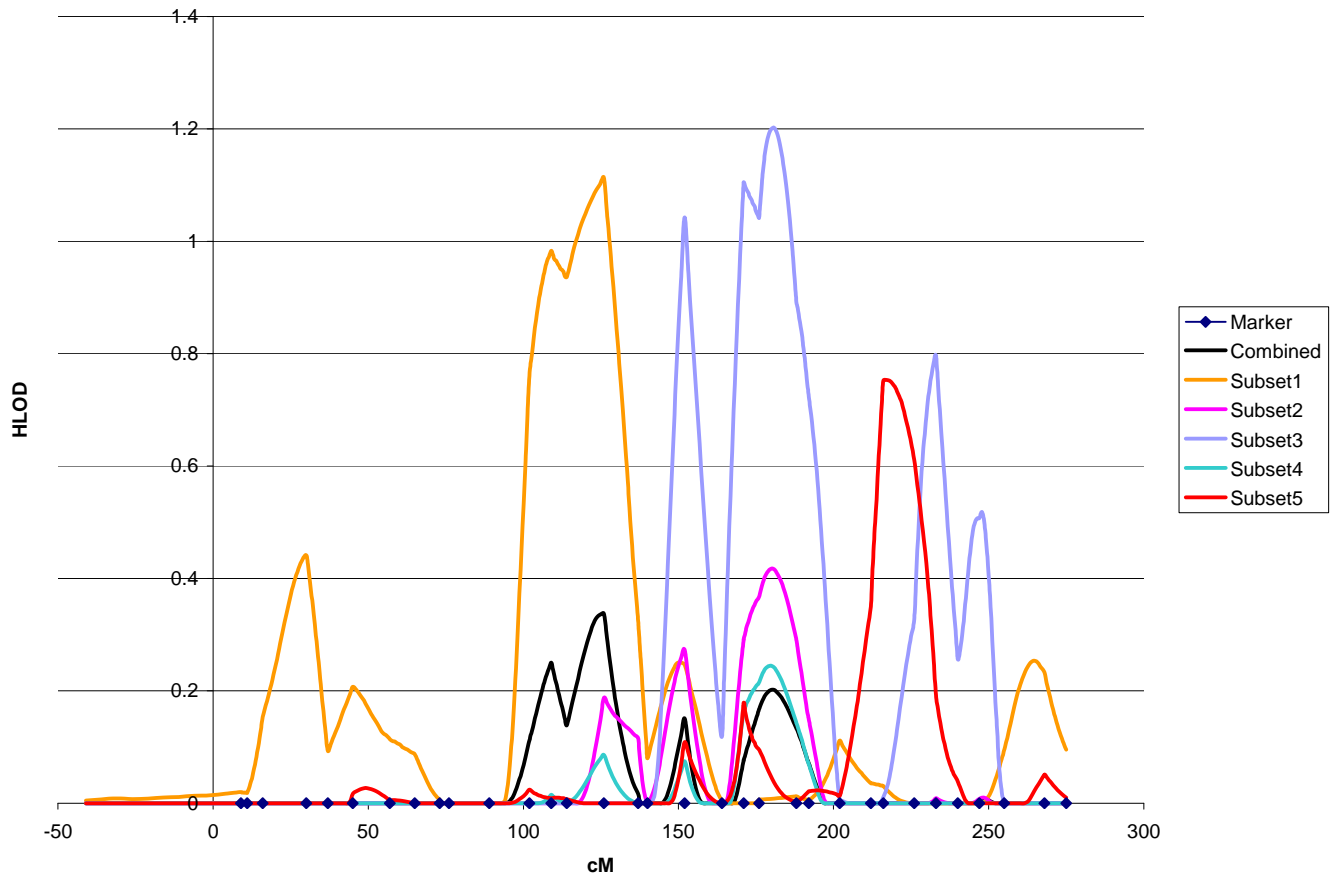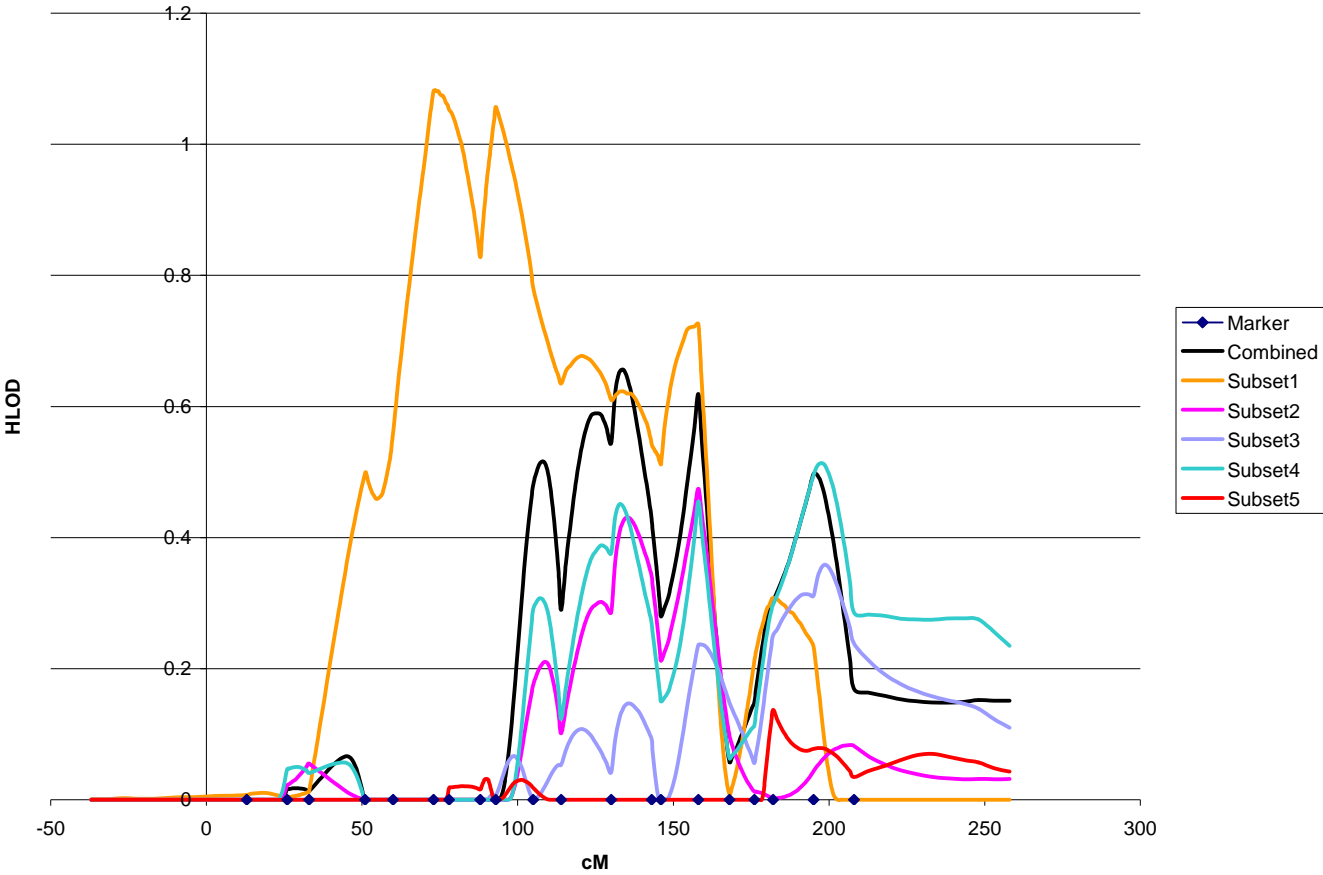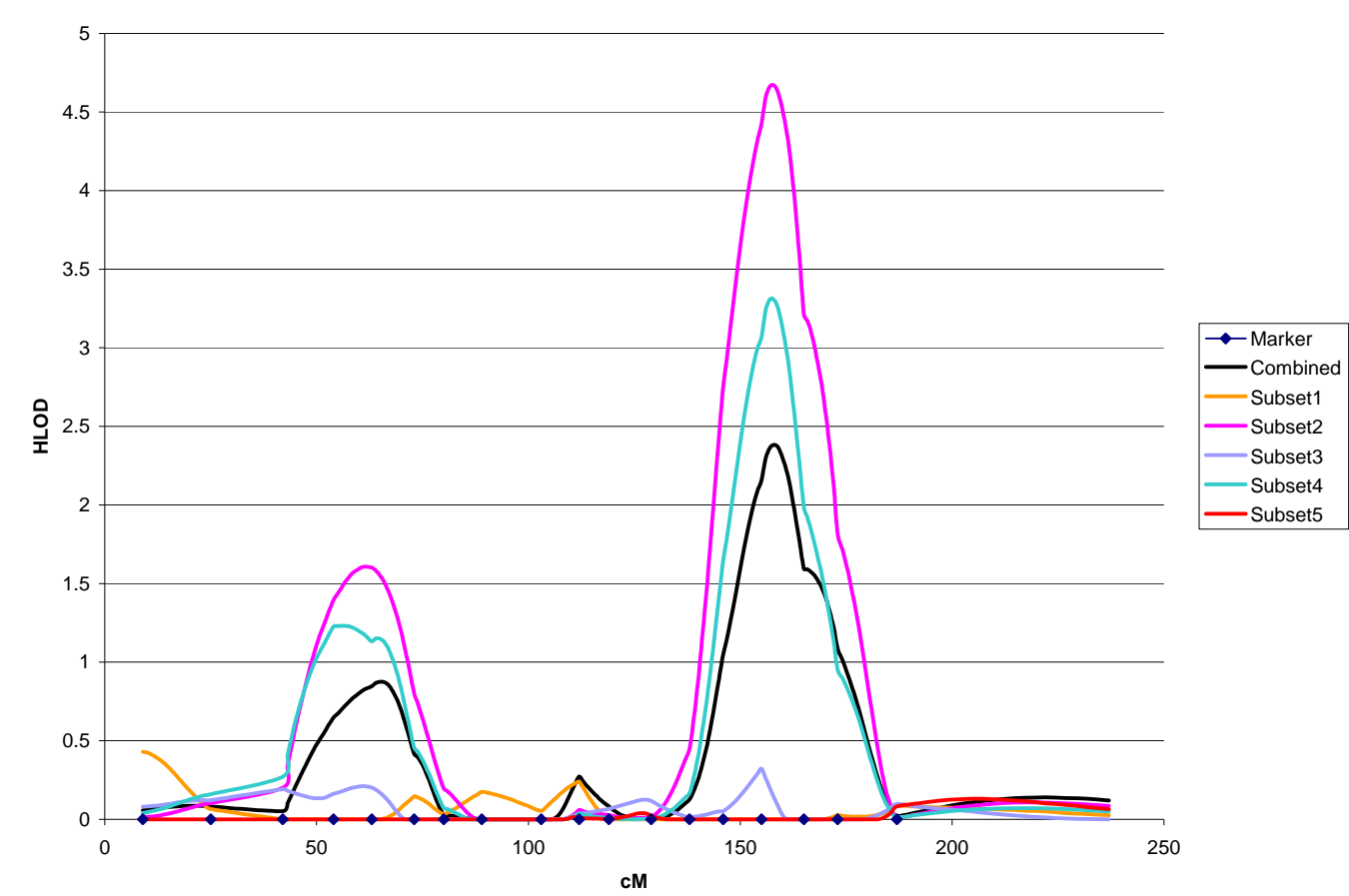Supplementary Figure 1. HLOD scores for subsets1-5 and the combined HLOD score across all families for chromosome 1. Subset 1 includes families with 2 or 3 affected relatives. Subset 2 includes famlies with 5 or more affected relatives in two or more generations. Subset 3 includes families with 4 or more affected in a sibship. Subset 4 includes 4 or more affected relatives in 2 or more generations. Subset 5 includes 4 or more affected relatives in a sibship and no other affected relatives. Subsets 1, 2, 4 and 5 are mutually exclusive.

Supplementary Figure 2. HLOD scores for subsets1-5 and the combined HLOD score across all families for chromosome 4.

Supplementary Figure 3. HLOD scores for subsets1-5 and the combined HLOD score across all families for chromosome 6.

Supplementary Table 1. Case and control weights used for weighted Cox regression analysis.

| Age Group | Number of Cases | Number of Controls | **Period Incidence** Incidence | Case Weights | Control Weights |
|---|---|---|---|---|---|
| | | | | | |
| | | | | | |
| 18-29 | 1 | 629 | 0.00005 | **1.2628** | **0.9996** |
| 30-34 | 4 | 337 | 0.00006 | **0.3466** | **1.0078** |
| 35-39 | 13 | 449 | 0.00019 | **0.3040** | **1.0202** |
| 40-44 | 19 | 562 | 0.00056 | **0.5493** | **1.0152** |
| 45-49 | 41 | 563 | 0.00128 | **0.4915** | **1.0370** |
| 50-54 | 52 | 513 | 0.00260 | **0.6397** | **1.0365** |
| 55-59 | 65 | 524 | 0.00524 | **0.7963** | **1.0253** |
| 60-64 | 85 | 378 | 0.00943 | **0.8114** | **1.0424** |
| 65-69 | 91 | 335 | 0.01435 | **0.8061** | **1.0527** |
| 70-79 | 83 | 769 | 0.08117 | **4.1662** | **0.6583** |

Supplemental Table 2a.  Risks for cancer are contrasted for carriers and noncarriers in families for which the risk haplotype could be identified versus families with unknown carrier status (which form the referent category).

| | Never Smoker | | | Light Smoker | | | Moderate Smoker | | | Heavy Smoker | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Non-carrier | 0 | NA | 0.99 | 1.08 | (0.31,3.83) | 0.90 | 0.83 | (0.41,1.65) | 0.59 | 0.83 | (0.54,1.29) | 0.41 |
| Carrier | 4.71 | (2.35,9.43) | <.0001 | 4.34 | (1.76,10.70) | 0.0014 | 2.51 | (1.53,4.13) | 0.0003 | 2.21 | (1.65,2.97) | <0.0001 |

Supplemental Table 2b.  Hazards ratios comparing carriers and noncarriers to individuals with unknown risk haplotypes (**with weights**)

| | Never Smoker | | | Light Smoker | | | Moderate Smoker | | | Heavy Smoker | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Non-carrier | 0 | NA | 1 | 0.80 | (0.19,3.39) | 0.90 | 0.79 | (0.40,1.56) | 0.50 | 0.69 | (0.48,0.99) | 0.044 |
| Carrier | 3.31 | (1.99,5.49) | <.0001 | 3.17 | (1.33,7.59) | 0.0014 | 1.49 | (0.98,2.25) | 0.063 | 1.35 | (1.06,1.73) | 0.015 |