Supplementary Online Content

Samadder NJ, Smith KR, Wong J, et al. Cancer risk in families fulfilling the Amsterdam criteria for Lynch syndrome. *JAMA Oncol*. Published online August 3, 2017. doi:10.1001/jamaoncol.2017.0769

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Diagnostic Guidelines for Lynch Syndrome[a]

Criteria Name	Criteria Specifics
Amsterdam I	Three relatives with colorectal cancer, one of which is a first-degree relative of the other two; colorectal cancer affecting more than one generation; at least one colorectal cancer diagnosed before age 50 years
Amsterdam II	Three relatives with HNPCC-related[b] cancers; one of which is a first degree relative of the other two; HNPCC-related cancer affecting more than one generation; at least one HNPCC-related cancer diagnosed before age 50 years

[a]Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW; American College of Gastroenterology. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223-262.

[b]HNPCC-related cancer sites included the colon, rectum, endometrium, ovary (including fallopian), sebaceous carcinoma, small bowel, ureteric or CNS gliomas (including glioblastoma and astrocytoma).

eTable 2. Number and Size of Families That Fulfilled Amsterdam Criteria and Number of Relatives Affected by CRC or HNPCC Related Cancer

	Amsterdam I[a]	Amsterdam II[b]
Families	59	202
Number of Individuals within core Amsterdam families affected by CRC or HNPCC-related cancer Male Female	199 105 94	694 305 389
Median age of CRC diagnosis (range)	60 (18, 95)	65 (18, 95)
Percent of all CRC in Utah	1.2%	2.6%
Total number of Endometrial cancer in families		113
Percent of all Endometrial cancer in Utah		1.77%

[a]Three relatives with colorectal cancer, one of which is a first-degree relative of the other two; colorectal cancer affecting more than one generation; at least one colorectal cancer diagnosed before age 50 years

[b]Three relatives with HNPCC-related[a] cancers; one of which is a first degree relative of the other two; HNPCC-related cancer affecting more than one generation; at least one HNPCC-related cancer diagnosed before age 50 years

eMethods. Detailed Methodology

Familial Risk Analysis: Familial risk was measured using standardized morbidity ratios (SMRs) or relative risk. SMRs in relatives using age- and sex-matched cancer rates were estimated from the UPDB as described previously[14]. All individuals in the UPDB genealogy, were assigned membership in one of 128 birth year, sex and birthplace-specific cohorts. Internal cohort-specific rates of colorectal and 20 extracolonic cancers were estimated for all 128 birth cohorts separately, by summing the number of individuals with the selected cancer in each cohort and dividing by the total number of UPDB individuals in the cohort. The observed numbers of cancer cases by site are counted, without duplication, in the set of relatives being considered. Exact one-sided Poisson probabilities were calculated under the null hypothesis that SMR = 1.0, 95% CIs are estimated assuming that the number of observed cases follows a Poisson distribution with mean equal to the expected number of cancers. The formula SMR = observed cancers/expected cancers in an unbiased estimator of risk. Cancers that were part of the Amsterdam diagnostic criteria were not evaluated in the probands as they were selected on the basis of having these particular cancers.