Supplementary Online Content

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eAppendix. Detail of Statistical Methodology for Calculation of Familial Risk

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. Detail of Statistical Methodology for Calculation of Familial Risk

Kinship analysis was conducted to address the familiality of colorectal cancer based on the site of index (probands) colorectal tumor. A specialized suite of software, “Kinship Analysis Tools”, (http://www.huntsmancancer.org/research/shared-resources/utah-population-database/kinship-analysis-tools) is an integrated set of programs developed at the University of Utah Huntsman Cancer Institute specifically to take advantage of the particular resources of the UPDB, including genealogies and linked cancer records. This software was used to estimate the recurrence risk in relatives of probands, over the time period that statewide Utah Cancer Registry records were available, by family relationship class (described below) using Cox proportional hazard models.23

Using this software suite, we determined the risk of cancer to child and adult relatives of cancer cases compared to population-based controls within categories of relationship: first-degree, including parents, children and siblings; second-degree, including grandparents/grandchildren, aunts/uncles, and nieces/nephews; and third-degree (first-cousins). The magnitude of familial risk was estimated from Cox proportional hazard models, adjusting for number of biological relatives, their degree of relatedness, and their person-years at risk as described.23 Random population controls with a follow-up year in Utah equal to or greater than the case year of diagnosis were selected from the UPDB and matched 10:1 to cases on sex and year of birth. Probands (patients with cancer of unknown primary diagnosed between 1980-2010) were excluded from the population pool used for control selection.

All relatives of cases and of matched controls with adequate follow-up information, who linked to a UPDB pedigree comprised of at least two generations, were systematically included in the calculations even if that relative had been counted
previously. For example, in families that contain more than one sibling with colorectal cancer, each case was included as a separate index case and risk among all siblings of each case calculated separately. This approach has been shown to lead to unbiased estimates of familial risk.\textsuperscript{7,24} As observations within families are non-independent, a robust Huber-White sandwich estimator of variance for clustered data was also incorporated\textsuperscript{7}.