A Case–Control Study of Levothyroxine and the Risk of Colorectal Cancer

Gad Rennert, M.D., Ph.D., Hedy S. Rennert, M.P.H., Mila Pinchev, M.D., and Stephen B. Gruber, M.D., Ph.D., M.P.H.

Supplementary Materials

Methods

Patients were eligible for participation in the MECC study if they had received a diagnosis of colorectal cancer (CRC) between May 31, 1998, and March 31, 2006, and lived in a geographically defined area of northern Israel. Control subjects were identified from the same source population using the Clalit Health Services (CHS) database. CHS is the largest health care provider in Israel and covered, during the study years, approximately 70% of persons older than 60 years. Health care coverage in Israel is mandatory and is provided by four groups akin to not-for-profit health maintenance organizations. Thus, all study participants (patients and control subjects) had similar basic health insurance plans and access to health services. Control subjects were individually matched to patients by year of birth, sex, residence (defined by primary clinic location), and ethnic group (Jewish vs. non-Jewish). Potential control subjects were excluded if they had a history of CRC. Participants provided written informed consent at the time of enrollment and were interviewed in person to obtain information about their personal and family history of cancer, reproductive history, medical history, medication use, and health habits, including a previously described dietary questionnaire (14). Diagnoses of CRC were made independently by the diagnosing hospitals and were confirmed by means of a standardized pathologic review by one pathologist.

Exposure Data

Data on levothyroxine and statin use were obtained from a question pertaining to all medications taken for at least 5 years, defined as long-term use. All aspirin use was recorded, including dose and duration of use, as was the use of female hormone replacement therapy. The association of daily aspirin use with risk of CRC was similar for 3 and 5 year durations. Daily aspirin use for at least 3 years was used in these analyses because it increased statistical power by including a larger number of aspirin users. Among daily aspirin users, 78.9% were using low-dose aspirin. Family history was defined as a report of colon or rectal cancer in at least one first-degree relative. Assessment of physical activity was based on a question on regular participation in sports activity (coded as yes or no). Ethnic group was determined by assessing participants' religious affiliation, self-described ethnic group, and the country of birth of their parents and grandparents. A validated food-frequency questionnaire adapted to the Israeli diet (16) was used to study the association of various dietary components with the risk of CRC. Vegetable consumption was categorized into two groups based on the median number of servings consumed per day in the control group (<5, 5+ servings per day). The lower category of consumption was used as the reference category. Colorectal cancer screening in Israel was uncommon during most of the study period and therefore screening frequency was found not to be a statistically significant variable. We did not have self-reported information about hypo- or hyperthyroidism.