INTRODUCTION There were over 14 million new cancer cases, and more than 30 million people living with cancer (within 5 years of diagnosis) worldwide in 2012.1 The overall age standardized cancer incidence rate was almost 25% higher in men than in women, with rates of 205 and 165 per 100,000, respectively.1 Male incidence rates varied approximately 5–fold across the different regions of the world, while those for females varied 3–fold.1 It has been estimated that at least a third of the most common cancers are related to lifestyle and as such are preventable.2 Individual modifiable lifestyle factors have been shown to be associated with cancer risk such as smoking,3 alcohol consumption,3 diet,2 physical activity,2 and anthropometry.4 People have a propensity to follow common behavioral patterns,5 and such lifestyle factors are often clustered, therefore, it seems logical to examine these lifestyle factors jointly. There is evidence mounting on the association of patterns of behavior, or combined lifestyle factors, to cardiovascular disease5,6 and diabetes,7 and more recently, to cancer types.8,9 Benefits of adhering to healthy lifestyles have been quantified specifically in relation to cancer risk in a prior study which assessed the association between concordance with World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) overall cancer prevention guidelines and subsequent cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort and reported a protective effect of adhering to the guidelines; nevertheless the effect varied among cancer types, showing the score worked well in some cancers but not for all cancers.10 Further investigations within the EPIC cohort include various health index associations with specific cancer sites (e.g., breast,11 colorectal,12 gastric13). In order to examine specific risk–related cancer subgroupings (i.e., alcohol–related cancers, tobacco–related cancers, obesity–related cancers, and, among women, reproductive–related cancers) within EPIC, an a priori healthy lifestyle index was created based on posited dietary components as previously proposed.5,7,11,14 Fiber, carbohydrates, fruits and vegetables, red and processed meats, and different fatty acids have all been posited to affect cancer risks.2,15,16 The healthy lifestyle index and its 5 components: smoking status, physical activity, alcohol consumption, diet, and body mass index (BMI), were used to assess associations with all cancer, and the alcohol–, tobacco–, obesity–, and reproductive–related cancer groupings. METHODS Study Population EPIC is a prospective cohort study conducted in 23 centers across 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom).17 The cohort of 521,330 healthy men and women were recruited from 1992 to 2000, to investigate the relationship between nutrition, dietary habits and lifestyle, and cancer incidence. Participants were aged between 25 and 70 years and enrolled from the general population, with exceptions for France (national health insurance scheme members), Utrecht and Florence (breast cancer screening participants), Oxford (health conscious, mainly vegetarian, volunteers), and some centers from Italy and Spain (blood donor participants). The rationale, study design, and methods for EPIC have been described in detail elsewhere.17 Ethical approval was obtained from participating centers and IARC ethics committees. All study participants gave informed consent. Data Collection and Follow–Up Participants completed validated country–specific questionnaires at baseline, including interviewer–administered diet histories or self–administered semi–quantitative food frequency questionnaires to measure usual intakes.18 The harmonized EPIC nutrient database was used to

estimate energy intake.19 Sociodemographic data, smoking history, alcohol consumption, and physical activity were obtained from lifestyle questionnaires, and anthropometric measurements taken, except for Oxford and France where measurements were self-reported.17 In Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the UK follow-up was performed through cancer registries. In France, Germany, and Greece, follow-up was performed through health insurance records, cancer/pathology registrations, and via participants and their next-of-kin. Follow-up commenced at date of enrolment and finished at date of cancer diagnosis, death, or at last complete follow-up (December 2004 to June 2010, depending on each center), whichever came first. Cancer incident cases were defined as first primary invasive tumors (coded using the 10th Revision of International Statistical Classification of Diseases). Cancer Subgroupings Alcohol-Related Cancers Colorectal cancer [C18–C20], female breast cancer [C50], upper aero-digestive (UADT) cancers (including cancer of the mouth [C01–C10 without C08=salivary gland], larynx [C32], pharynx [C11–C14], esophagus [C15]), and liver cancer [C22–C24].2,3 Tobacco-Related Cancers Upper aero-digestive cancers (including cancer of the mouth [C01–C10 without C08=salivary gland], larynx [C32], pharynx [C11–C14], esophagus [C15]), liver [C22–C24], pancreas [C25], bladder [C67], kidney [C64, C65], cervix [C53], stomach [C16], trachea [C33], lung [C34], acute myeloid leukemia [C92], and colorectum [C18–C20].3 Obesity-Related Cancers Esophagus [C15], pancreas [C25], colorectum [C18–C20], breast (after menopause) [C50], endometrium (lining of the uterus) [C54], kidney [C64, C65], thyroid [C73], and gallbladder [C23].2 Female Breast and Reproductive-Related Cancers Breast (after menopause) [C50], vulva [C51], vagina [C52], cervix [C53], uterine [C54–C55], ovary [C56] and other female genital organs [C57–C58]. The original EPIC cohort comprised 521,330 men and women; 477,312 after the exclusion of participants with prevalent cancers (23,785) or missing follow-up information (4380), missing dietary or lifestyle questionnaires (6253), and those in the top or bottom 1% of the ratio of energy intake to energy requirement (9600). The present study was based on data from 391,608 men and women, following exclusions of those that were not primary malignant cancers (10,392), and those with missing data for the components of the lifestyle index (75,312), including all participants from Umea in Sweden, and Norway, where information on physical activity was not collected. Index Construction Score for Diet Intakes of 6 dietary factors were combined for the diet score: cereal fiber, red and processed meat, the ratio of polyunsaturated to saturated fat, margarine (as a marker for industrially produced trans-fats), glycemic load, and fruits and vegetables. The linear regression residuals of each dietary component on total energy intake were grouped into country-specific deciles and scored from 0 to 9 (inverse for red/processed meat, trans-fat, and glycemic load), with 0 being least healthy consumption (for margarine there was a non-consumers category). The individual scores were summed to a total diet score, and then categorized into quintiles.11 Score for Health Index The overall healthy lifestyle index was determined by assigning scores of 0 to 4 to each individual variable category, for which a higher point value indicates a healthier behavior.11 The healthy lifestyle index ranged from 0 to 20. Healthiest behavior was defined as never smoking (never smoked=4, ex-smokers quit>10 years=3, ex-smokers quit≤10-years=2, current smoking≤15cigarettes/day=1, current smoking>15cigarettes/day=0), low consumption of alcohol (