Glycosylated hemoglobin and risk of colorectal cancer and adenoma (United States)

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Received 12 November 1998; accepted in revised form 22 April 1999

Key words: colorectal neoplasms, glycosylated, hemoglobin A, United States, women.

Abstract

Objectives: The consistently observed epidemiologic associations of obesity and physical activity with colorectal cancer and precursor adenoma risk suggest that insulin and glucose control may be contributory. We evaluated the association of glycosylated hemoglobin (HbA1c), a clinical indicator of average glycemia over the previous 2 months, and possibly, indirectly, a marker of average blood insulin level, with colorectal carcinogenesis.

Methods: Among women in the Nurses’ Health Study, who provided blood in 1989–90 and were diagnosed subsequently in 1989–94, we included 79 colorectal cancer cases and 156 matched controls, and 201 distal colorectal adenoma cases and 201 matched controls. HbA1c concentrations in red blood cells were determined blindly by turbidometric immunoinhibition. Odds ratios (OR) and 95% confidence intervals (CI) were estimated from conditional logistic regression models.

Results: HbA1c level did not significantly differ between colorectal cancer cases (median 5.5%) and controls (5.5%, p = 0.5), although a small difference between adenoma cases (5.6%) and controls (5.5%, p = 0.06) was noted. Compared to the lowest tertile of HbA1c (median 5.2%), women in the middle (median 5.5%, OR = 1.2, CI = 0.6–2.5) and upper (5.8%, OR = 1.2, CI = 0.6–2.7) tertiles were not at an increased risk for colorectal cancer. A modestly elevated risk of distal colorectal adenoma in the upper (median 5.8%, OR = 1.4, CI = 0.9–2.3) versus lower (median 5.3%) tertile could not be excluded. These associations were not appreciably altered after adjusting for known and suspected colorectal cancer risk factors.

Conclusion: Over the range of levels observed in this relatively small sample of middle-aged women, prediagnostic HbA1c does not clearly predict colorectal cancer and adenoma risk.

Introduction

Higher body mass index (BMI) [1–5] and physical inactivity [1, 5–7] have consistently been found to be associated with an increased risk for colorectal cancer and precursor adenoma in epidemiologic studies. Obesity, more specifically central adiposity, is correlated with insulin resistance [8], and the associations of colorectal cancer and adenoma with obesity are stronger in men, who generally have a higher prevalence of central obesity, than in women [2, 7]. Waist-to-hip ratio, an indicator of central adiposity, is also associated with colorectal cancer risk [2]. Physical activity reduces plasma glucose and insulin levels by reducing adiposity [7] and increasing insulin sensitivity in muscle [9]. In recent studies, diabetics appear to be at a modestly increased risk for colorectal cancer in several [10–18], but not all [19] studies. Associations between newly diagnosed non-insulin-dependent diabetes and sigmoid colon adenomas [20], and between high blood glucose concentrations and colorectal carcinoma in situ [21], also have been observed. These observations indirectly suggest that glucose, through its action on production of insulin and other growth factors or through serving as
an energy source for colon cells, and insulin control may be important in colorectal carcinogenesis [22, 23].

To evaluate the association of glycemic control and possibly, indirectly, insulin level to colorectal cancer risk, we measured prediagnostic glycosylated hemoglobin (HbA1c) in colorectal cancer and adenoma cases and controls nested in the prospective Nurses' Health Study. HbA1c, formed from the attachment of a molecule of glucose to the last amino acids of the $\beta$ chain of hemoglobin A, is a clinical indicator of average glycemia over the past 2 months, and possibly a marker for average blood insulin level.

Materials and methods

Study population

Cases and controls were drawn from among participants in the Nurses' Health Study, an ongoing prospective study of 121,700 US female registered nurses. Details of the design and follow-up of this cohort have been described previously [24]. At enrollment in 1976 the women, who were 30–55 years old, completed a mailed questionnaire providing information on risk factors for cancer and cardiovascular disease. A semi-quantitative food-frequency questionnaire was added in 1980. Biennially, updated exposure and disease information was collected by mail, including reports of endoscopy and colon cancer and polyp diagnosis, and dietary information was updated in 1984, 1986, 1990, and 1994. In 1989 through 1990, 32,826 participants provided a blood specimen. After receipt by overnight courier the chilled heparinized blood was centrifuged, aliquoted into plasma, erythrocytes, and Buffy coat, and stored in continuously monitored liquid nitrogen freezers.

Selection of colorectal cancer cases and controls

Incident colorectal cancers reported on the 1990, 1992, or 1994 questionnaires were confirmed to be adenomatous by review of histopathologic reports and were classified by location (proximal or distal colon, or rectum), size ($<1$, $\geq1$ cm), and histology (villous, tubulovillous, tubular); hyperplastic and other non-adenomatous polyps were excluded. Because most of the endoscopies performed were limited to the distal colon, and could not detect proximal colon adenoma, we included only adenomas of the distal colon and rectum. Eligible women were those who supplied a blood sample in 1989–91, had a sigmoidoscopy or colonoscopy after providing a blood sample (1989–94), and were free from diagnosed cancer (except non-melanoma skin cancer) before endoscopy. Forty-eight cases were diagnosed $\leq1$ year after blood draw, 51 cases $>1$–2 years, 48 cases $>2$–3 years, 38 cases $>3$–4 years, and 16 cases $>4$ years after blood draw. Controls were matched to cases on endoscopy during the same 2-year period, birth year, indication for endoscopy (routine screening, family history, or gastro-intestinal symptoms), time period of first or most recent endoscopy excluding the one in the current time period, month and year of blood draw, and fasting status. A total of 201 matched pairs were included in the analysis.

HbA1c assay

HbA1c was determined (blinded to case status) by turbidometric immuno-inhibition in red blood cells using the Hitachi 911 analyzer (Boehringer Mannheim). The within-run imprecision of the assay, reflected by the coefficient of variation, for HbA1c values of 5.6% and 9.6% was less than 2.5%. The day-to-day variability for over a 1-year period at these two levels was less than 5%. The mean intra-pair coefficients of variation calculated from blinded quality control samples were 2.7% and 1.5% for the colorectal cancer and distal colorectal adenoma runs, respectively.

Assessment of other factors

Mean values were computed from the 1980 through 1990 questionnaires for BMI (weight in kg/square of height in m), physical activity (MET-hours/week), regular aspirin use ($2+\text{ days/week}$), cigarette smoking (pack-years),