

Research Article

Measured Body Mass Index in Adolescence and the Incidence of Colorectal Cancer in a Cohort of 1.1 Million Males

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Abstract

Background and Aims: The increasing prevalence of adolescent obesity affects adult health. We investigated the association of adolescent overweight with colorectal cancer incidence in a large cohort of males.

Methods: Body mass index (BMI) was measured in 1.1 million Jewish Israeli males who underwent a general health examination at ages 16 to 19 between 1967 and 2005. Overweight was defined as BMI \geq 85th percentile of the standard U.S. distribution in adolescence. Colorectal cancer was identified by linkage with the Israel National Cancer Registry up to 2006. The mean follow-up period was 17.6 ± 10.9 years, reflecting 19.5 million person-years. Cox proportional hazards modeling was used.

Results: The prevalence of adolescent overweight increased from 9.9% to 16.8% in the first 10 and last 10 annual examination cohorts. Colon ($n = 445$) and rectal cancer ($n = 193$) cases were detected. Overweight predicted an increased risk of colon cancer [HR = 1.53; 95% confidence interval (CI), 1.17–2.02, $P = 0.002$] but not of rectal cancer (HR = 1.09; 95% CI, 0.38–1.73, $P = 0.72$). The risk was greatest for nonmucinous adenocarcinoma of the colon (HR = 1.68, 95% CI, 1.26–2.23, $P = 0.001$). The association of BMI \geq 85th percentile with colon cancer was even more pronounced in analyses that were restricted to men followed until at least 40 years of age [$N = 367,478$; HR = 1.75 (95% CI, 1.33–2.3, $P < 0.001$)].

Conclusions: Adolescent overweight is substantially associated with colon cancer incidence in young to middle-aged adults.

Impact: These long-term sequelae add to the urgency to seriously address increasing childhood and adolescent obesity with its attendant increasing population impact. *Cancer Epidemiol Biomarkers Prev*; 20(12); 2524–31. ©2011 AACR.

Introduction

Colorectal cancer (CRC) is the second leading cause of death from cancer among adults in the United States (1) as well as in Israel (2). Multiple cohort and case-control studies and meta-analyses consistently report that adult obesity is associated with an increased risk of colon cancer in men whereas the evidence is less consistent for rectal cancer and for women (3–5).

On the other hand, few studies have addressed the impact of adolescent overweight and obesity on the incidence of CRC cases later in life (6–13). The data are inconsistent as some of the studies included few incident

cases, whereas other studies included self-reported, rather than measured body mass index (BMI).

According to the U.S. Preventive Services Task Force, adolescent overweight is defined as an age- and gender-specific BMI between the 85th and 95th percentiles, and obesity is defined as an age- and gender-specific BMI at the 95th percentile of BMI (14). During the past 3 decades, childhood and adolescent obesity have increased 3- to 6-fold, with the rate of increase dependent on age, gender, and ethnicity (15). Recently, it was reported that 32% of U.S. adolescents were at or above this 85th percentile value (16).

In the current study, we addressed the association of BMI measured in late adolescence with incident CRC later in life in a cohort of 1.1 million Jewish Israeli males with 19.5 million person-years of follow-up.

Subjects and Methods

Study population

Israeli adolescents were invited to recruitment centers, predominantly at age 17, for an obligatory medical board examination to assess their suitability for military service. We restricted the analysis to Jewish males who were

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examined between 1967 and 2005 and were aged 16 to 19 years (mean age: 17.3 ± 0.4) when examined. They were followed up by data linkage for cancer incidence until the end of 2006 by data linkage. A subcohort included only those who were born between 1947 and 1966, such that their minimum age at the end of follow-up was at least 40 years. The main cohort and the subcohort comprised 1,109,864 and 367,478 male adolescents, respectively.

Data collection

Body mass index. Height and weight, as well as sociodemographic and clinical data, were measured and recorded during the obligatory medical board examination. Subjects were measured barefoot wearing only a shirt and underwear. The measurements were conducted by trained medical personnel using a beam balance and stadiometer. BMI was calculated as weight (in kilograms) divided by height (in meters squared). Excessive body weight among adolescents was defined in relation to the 2000 United States CDC BMI-for-age growth charts, internationally used for reference purposes, as at or above the age- and sex-specific 85th percentile of BMI (14,17). Because during adolescence, the threshold for overweight is dynamic (i.e., at age 16.0 years, the threshold is 24.2 kg/m^2 ; 8 months later, 24.8 kg/m^2 ; and at 17.3 years, 25.2 kg/m^2 ; and our study population was aged 16.0–19.9 years), we preferred not to use the traditional WHO classification for overweight and obesity. The average age at measurement in our cohort was 17.3 years (208 months). At this age, the 85th percentile of Israeli adolescents in our sample in the year 2000 was 25.14 kg/m^2 , very close to the 85th percentile U.S. CDC threshold (25.18 kg/m^2).

Because the cohort of BMI \geq 95th percentile included only a few cases of CRC ($n = 22$), we grouped the BMI into those with or without excessive body weight (\geq 85th vs. $<$ 85th percentile) as well as into quintiles [BMI (kg/m^2): Q1, ≤ 19.01 ; Q2, 19.02–20.33; Q3, 20.34–21.67; Q4, 21.68–23.62; Q5, ≥ 23.63].

In 43,347 persons, we had a follow-up measure in adulthood. For purposes of assessment of tracking of BMI from adolescence to adulthood, we grouped this subsequent measure according to the WHO classification (<18 , 18–24.9, 25–29.9, 30–34.9, and $\geq 35 \text{ kg/m}^2$).

Ascertainment of CRC incidence

We linked the cohort to the Israel National Cancer Registry (INCR) by way of the personal identification number given to all Israeli citizens at birth or immigration. The INCR, a population-based registry in operation since 1960, meets internationally accepted requirements for the coding system (ICDO-Version 3) and completeness of data. Reporting is mandatory since 1982; coverage exceeds 95%, and has been excellent since the inception of the registry in the 1960s (2). We included only CRCs, with a histologic report of adenocarcinoma (codes 80003, 80103, 81403, 82103, 82613, 82633, 84813, 84803, and 84903), of the colon (codes

C18.0–18.9), and of rectum (codes C19.9 and C20.9), excluding all other histology codes (97313, 96803, 96873, and 96993). Mucin-producing and signet ring tumors were classified as mucinous tumors (codes 84813, 84803, and 84903).

Covariate data

Covariate baseline adolescent data included year of birth, country of origin (which we defined as father's place of birth or grandfather's place of birth if father was Israeli born), socioeconomic status classified according to the settlement/city of residence on a 1 to 10 scale (Central Bureau of Statistics), immigration status, age at immigration, years of schooling, and place of residence (rural or urban). About 12% of the invited population was not examined; these persons were excluded. BMI was missing in 3.4% of the examined population; these persons were also excluded. Among the 1,109,864 adolescents included in the analysis, data were missing in 0.1% for education, 0.3% for origin, 0.9% for socioeconomic status, and 1.1% for place of residence.

Statistical analysis

The characteristics of the participants are presented as arithmetic means (\pm SD), or in the case of characteristics with skewed distributions, as medians and interquartile ranges. Cox proportional hazards models were used to test for associations between the baseline adolescent BMI and time to CRC diagnosis, adjusting for age at examination, year of birth, country of origin (grouped as Israel, Asia, Africa, Europe), urban or rural place of residence, immigration status, years of schooling, socioeconomic status of the place of residence, and height. BMI was treated either as a dichotomous variable (overweight compared with normal) or grouped by quintiles. Log minus log plots for each variable were inspected to verify the assumption of proportionality of the hazards. Cumulative incidence curves for CRC according to BMI at baseline (\geq 85th and $<$ 85th percentile) were prepared for colon and rectal cancers, adjusted in Cox regression models for the above baseline covariates. The population attributable risk percentage (PAR%) of colon cancer was calculated in relation of being overweight or obese (\geq 85th percentile) as follows: $\text{PAR}\% = \frac{\text{Pe}(\text{HR}-1)}{\text{Pe}(\text{HR}-1)+1} \times 100$, in which HR is the adjusted HR of the relationship between being overweight or obese (\geq 85th percentile) and having colon cancer and Pe is the prevalence of being overweight or obese (\geq 85th percentile) in the control population. Analyses were conducted with SPSS software, version 19.

Ethics

The Israel Defense Forces Medical Corps Institutional Review Board approved the study. After data linkage at the INCR, personal identifiers were permanently deleted from the computer file so that all analyses were undertaken on anonymous records.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the participants; 82.6% were Israeli born and 88.4% were urban dwellers. In 939,471 participants (84.6%), the BMI was measured at age 17 years. Excessive body weight (≥ 85 th age-, sex-specific U.S. CDC percentile) was noted in 12.5% of the adolescents, 9.9% among the first 10 annual examination cohorts, and 16.8% in the last 10 cohorts, increasing to 18.3% in the last 3 cohorts. The follow-up ranged from 0.5 to 40 years, with a mean of 17.6 ± 10.9 years.

Characteristics of the CRC cases

Six hundred and thirty-eight CRC cases were identified during the follow-up period; 445 (69.7%) of which were

colon cancer and 193 (30.3%) rectal cancer. Of all the CRC cases, 537 (84.2%) cases were nonmucinous adenocarcinoma and 101 (15.8%) were mucinous adenocarcinoma. The mean age at CRC diagnosis was 43.2 ± 8.7 years (range: 18.7–57.3 years).

BMI in adolescence and CRC

As compared with adolescents with a baseline BMI less than 85th percentile, adolescents with a BMI ≥ 85 th percentile had a significantly increased risk for colon cancer (HR = 1.53; 95% CI, 1.17–2.0, $P < 0.001$) but not for rectal cancer (HR = 1.09; 95% CI, 0.68–1.73, $P = 0.72$; Table 2). Analysis of the risk according to baseline BMI grouped by quintiles (Table 3) showed that the increased risk was restricted to the highest quintile (HR = 1.69; 95% CI, 1.24–2.29, $P = 0.001$). Figure 1 shows the cumulative incidence curves according to baseline BMI separately for colon and rectal cancer. The excess risk for CRC associated with BMI ≥ 85 th percentile at adolescence was most evident for nonmucinous colon cancer (HR = 1.68, 95% CI, 1.26–2.23, $P = 0.001$) but not for the mucinous cancer (HR = 0.94; 95% CI, 0.47–1.86, $P = 0.86$).

Analyses were repeated among individuals who were at least 40 years of age by the end of follow-up. Of these, 9.2% were overweight (BMI ≥ 85 th percentile). Their mean age at the end of follow-up was 48.1 ± 5.2 years and their mean follow-up period was 30.7 ± 5.2 years with a total of 11,293.526 person-years of follow-up. Of the 561 CRC cases detected, 390 (69.5%) were located in the colon and 171 (30.5%) were sited in the rectum; 476 (84.8%) were nonmucinous and 85 (15.2%) were mucinous adenocarcinoma. The mean age at diagnosis was 46.6 ± 6.5 years.

Table 4 shows the results of the Cox proportional hazards analysis. In this cohort, the risk for colon cancer associated with BMI ≥ 85 th was even higher (HR = 1.75; 95% CI, 1.33–2.30, $P < 0.001$) as was the risk for nonmucinous colon cancer (HR 1.86; 95% CI, 1.38–2.50, $P < 0.001$). Here again, the increased risk was restricted to the highest quintile (HR = 1.72; 95% CI, 1.24–2.38, $P = 0.001$). Mean age at CRC diagnosis did not differ between those with BMI ≥ 85 th percentile in adolescence and those with BMI < 85 th percentile (47.2 ± 5.8 vs. 46.5 ± 6.63 years, respectively; $P = 0.43$).

To avoid possible bias due to underweight, we also repeated the analysis after excluding persons in the less than 5th percentile (49,998 persons; 25 CRC cases). The HRs for both colon and rectal cancer among adolescents with BMI ≥ 85 th percentile as compared with BMI < 85 th percentile [colon cancer: HR 1.51 (95% CI, 1.15–1.97), $P = 0.003$; rectal cancer: HR 1.10 (95% CI, 0.69–1.760), $P = 0.67$] was not different from the primary analysis without excluding the underweight category.

In a sub cohort of 43,347 persons, we had a follow-up BMI measure in adulthood. The mean age at first measure (baseline) was 17.1 ± 0.4 years and the mean age at the second measurement was 30.4 ± 5.2 years. Overweight during adolescence (≥ 85 th percentile) predicted overweight (BMI ≥ 25 kg/m²) during adulthood in 88.9% of

Table 1. Baseline characteristics of the study cohort of Israeli males examined between 1967 and 2005 and followed up to 2006

Total cohort	
<i>N</i>	1,109,864
<i>Age at BMI measurement</i>	
Mean age \pm SD, y	17.3 \pm 0.43
16 y, n (%)	90,714 (8.2)
17 y, n (%)	939,471 (84.6)
18 y, n (%)	63,536 (5.7)
19 y, n (%)	16,143 (1.5)
<i>BMI at measurement</i>	
BMI < 85 th percentile	
n (%)	971,393 (87.5)
Mean BMI, kg/m ²	20.6 \pm 2.05
BMI ≥ 85 th percentile	
n (%)	138,471 (12.5)
Mean BMI, kg/m ²	26.9 \pm 2.87
<i>BMI by quintiles</i>	
Q1 (≤ 19.01 kg/m ²)	17.9 \pm 0.86
Q2 (19.02–20.33 kg/m ²)	19.7 \pm 0.38
Q3 (20.34–21.67 kg/m ²)	21.0 \pm 0.38
Q4 (21.68–23.62 kg/m ²)	22.5 \pm 0.56
Q5 (≥ 23.63 kg/m ²)	26.4 \pm 2.87
<i>Place of residence (%)</i>	
Urban	88.4
Rural	12.5
<i>Immigration (%)</i>	
Israeli born	82.6
Immigrants	17.4
<i>Origin (%)</i>	
Europe	41.7
Asia	26.6
Africa	26.1
Israel	5.2
<i>Years of follow-up</i>	
Mean \pm SD (range)	17.6 \pm 10.9 (0.5–40)
Cumulative (person-years)	19,564,191

Table 2. Cox proportional HRs for CRC, according to baseline BMI (<85th or >85th percentile) in 1,109,864 males examined between 1967 and 2005 and followed up through 2006

Cancer (n)	Adjusted HR (95% CI) ^a	P
Colon (445)		
BMI < 85th (380)	1.0 (referent)	0.002
BMI ≥ 85th (65)	1.53 (1.17–2.00)	
Rectum (193)		
BMI < 85th (173)	1.0	0.723
BMI ≥ 85th (20)	1.09 (0.68–1.73)	
Colorectal, nonmucinous (537)		
BMI < 85th (461)	1.0	0.002
BMI ≥ 85th (76)	1.49 (1.16–1.90)	
Colon, nonmucinous (368)		
BMI < 85th (310)	1.0	0.001
BMI ≥ 85th (58)	1.68 (1.26–2.23)	
Colorectal, mucinous (101)		
BMI < 85th (92)	1.0	0.869
BMI ≥ 85th (9)	0.94 (0.47–1.88)	

^aCox proportional analysis adjusted for year of birth, age at BMI measurement, country of origin, residence (rural or urban), immigration status, socioeconomic status, and height.

subjects. Among adolescents that were not overweight (<85th percentile), 60.6% remained so in adulthood (BMI < 25 kg/m²).

Discussion

The current study in a large cohort with a long-term follow-up points toward a number of important observations: First, we have shown that overweight as measured in late adolescence (rather than retrospectively reported in adulthood) was associated with a substantially increased risk of colon, but not rectal cancer, in young to middle-aged adulthood. Second, the increased risk associated with increased BMI was restricted to the highest quintile. And finally, the increased risk associated with higher BMI was restricted to the nonmucinous cancers.

The association between adult obesity and the risk of CRC has been studied extensively in several meta-analyses (3–5). Larsson and Wolk (5) reported that obesity was significantly positively associated with colon cancer risk in both men and women and with rectal cancer risk in men. The association between obesity and risk of cancer in men was stronger for colon cancer than for rectal cancer. Moghaddam and colleagues (4) reported that individuals with a BMI ≥ 30 kg/m² had a 40% greater risk of CRC than individuals with a BMI < 25 kg/m² [relative risk (RR) = 1.40; 95% CI, 1.31–1.51]. In another recent meta-analysis, Renehan and colleagues (3) reported that the RR for colon and rectal cancers in men was 1.24 (95% CI, 1.24–1.28) and 1.09 (95% CI, 1.06–1.12), respectively.

In contrast to the extensive data on the association between adult obesity and the risk for CRC, only a few studies have examined the association of early life BMI

and later CRC and even fewer studies relate to BMI (measured or reported) in adolescence or young adulthood (6–13). It appears that our study has more incidence cases of CRC than in all previous studies in adolescents combined. The largest study that is comparable with ours is a follow-up of participants in a tuberculosis screening program in Norway (8). They reported that both males and females in the highest BMI category (>85th percentile) had an increased risk of death from CRC [males: RR = 2.1 (95% CI, 1.1–4.1); females: RR = 2.0 (95% CI, 1.2–3.5)], but data were not reported separately for cancers of the colon and rectum. In our study, increased BMI in adolescence was not associated with rectal cancer, consistent with the finding of Campbell and colleagues, who found a stronger association of recalled BMI at 20 years for colon than for rectal cancer (9). As stated earlier, meta-analyses on adult obesity and CRC report that the association is weaker with rectal cancer (3, 5).

Larsson and Wolk (5), in a large meta-analysis, reported that the association with BMI between cancer sites showed that the RR was statistically significantly higher for colon cancer than for rectal cancer ($P < 0.001$ in men and $P = 0.01$ in women), as evident in our study. Another meta-analysis showed that increased leisure-time physical activity, which is related to improved insulin sensitivity was associated with a reduced risk of colon cancer but not of rectal cancer (18). This may suggest that insulin resistance, hyperinsulinemia, and other factors related to obesity may be stronger risk factors for colon than for rectal cancer.

In a subgroup of patients with CRC, there is inactivation of genes required for repair of mismatches in DNA. The inactivation can be inherited, as in hereditary

Table 3. Cox proportional HRs for CRC, according to baseline BMI (divided into quintiles) in 1,109,864 males examined in 1967 to 2005 and followed up through 2006

Cancer (n)	Adjusted HR (95% CI) ^a	P
Colon (445)		
Quintile 1 (68)	1.0 (referent)	
Quintile 2 (89)	1.10 (0.80–1.53)	0.534
Quintile 3 (97)	1.14 (0.93–1.57)	0.412
Quintile 4 (78)	0.96 (0.69–1.33)	0.798
Quintile 5 (113)	1.69 (1.24–2.29)	0.001
Test for trend by quintile		0.001
Rectum (193)		
Quintile 1 (42)	1.0	
Quintile 2 (43)	0.82 (0.53–1.27)	0.367
Quintile 3 (44)	0.86 (0.56–1.32)	0.488
Quintile 4 (29)	0.52 (0.32–0.85)	0.009
Quintile 5 (35)	0.86 (0.54–1.34)	0.491
Test for trend by quintile		0.125
Colorectal, nonmucinous (537)		
Quintile 1 (89)	1.0	
Quintile 2 (113)	1.10 (0.83–1.46)	0.509
Quintile 3 (117)	1.07 (0.80–1.14)	0.652
Quintile 4 (93)	0.85 (0.63–1.13)	0.278
Quintile 5 (125)	1.43 (1.09–1.89)	0.011
Test for trend by quintile		0.004
Colorectal, mucinous (101)		
Quintile 1 (21)	1.0	
Quintile 2 (19)	0.57 (0.29–1.13)	0.109
Quintile 3 (24)	0.90 (0.50–1.63)	0.741
Quintile 4 (14)	0.55 (0.28–1.09)	0.088
Quintile 5 (23)	1.12 (0.62–2.02)	0.708
Test for trend by quintile		0.132

^aCox proportional analysis adjusted for year of birth, age at BMI measurement, country of origin, residence (rural or urban), immigration status, socioeconomic status, and height.

non-polyposis colon cancer (HNPCC) or acquired, as in tumors with methylation-associated silencing of a gene that encodes a DNA mismatch repair protein (19). The loss of mismatch repair function is associated with microsatellite instability (MSI; refs. 19, 20). The MSI status of the tumor is considered as a predictor of the response to fluorouracil-based adjuvant chemotherapy and survival (21, 22).

Campbell and colleagues (7) reported a case-control study of BMI and CRC risk in relation to tumor MSI status. Their data suggested that recent BMI and adult weight gain were associated with the risk of microsatellite-stable colorectal tumors but not with the risk of MSI-high colorectal tumors. In our study, the MSI status of incident cases was not available. However, tumor histology of mucinous cancer is highly correlated with MSI-high tumor status and serves as surrogate marker for MSI-high tumors (23–25, 26, 27). We report that the increased risk associated with increased BMI was evident only for the nonmucinous cancer, hence our data are consistent with

those of Campbell and colleagues. Engeland and colleagues (28) studied around 2,000,000 Norwegian men and women aged 20 to 74, the mean age at BMI measurement being 44 years and the mean age at CRC diagnosis being 70 years. In contrast with our findings, they reported that the association of BMI with CRC was more pronounced for mucinous adenocarcinomas.

Because in our young cohort with up to 40 years of follow-up, most of the CRC cases occurred at a young age (mean age at diagnosis was 43.2 ± 8.7 years), it is probable that the CRC cases in this cohort are enriched in cases with a familial background. We did not have data about the family history. This, however, should not bias our findings as Campbell and colleagues reported that men both with and without clinically defined familial risk of cancer were at similar risks of CRC if overweight or obese (9). A recent survey by our group reported on the histologic and pathologic characteristics of CRC in Israel (29). As compared with CRC among patients older than 50 years, CRC among patients younger than 50 years tend to be more

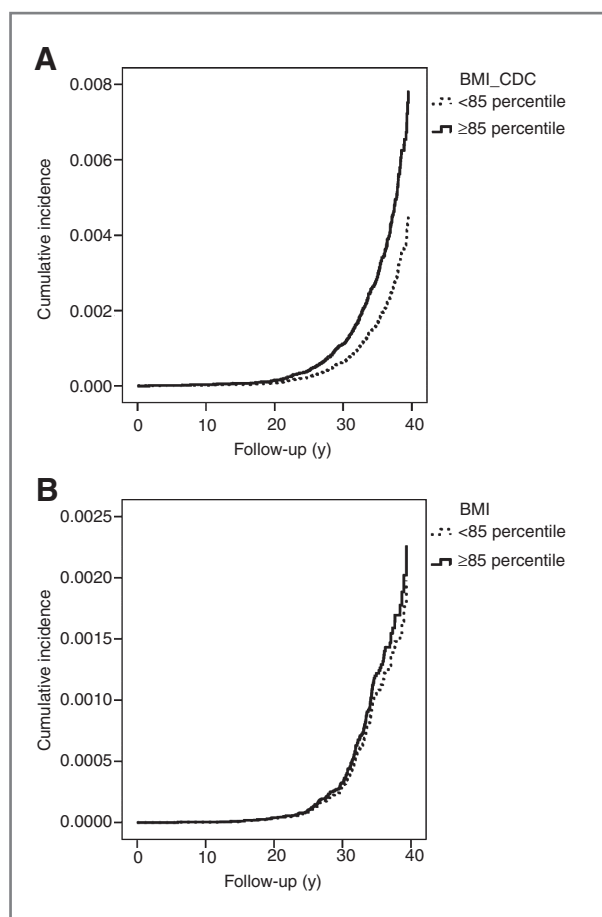


Figure 1. Cumulative incidence of colon (A) or rectal cancer (B), according to adolescent BMI (≥ 85 th or < 85 th percentile). A, cumulative incidence of colon cancer according to BMI in adolescence. B, cumulative incidence curves of rectal cancer according to BMI in adolescence.

mucinous (14.3% vs. 10.7%, $P < 0.001$) and were located more often in the rectum (38.0% vs. 27.2%, $P < 0.001$; ref. 29). As the association between overweight in adolescence and increased HR for cancer was evident for the nonmucinous (but not for the mucinous cancer) and for colon cancer (but not for rectal cancer), we expect that as the cohort ages, the impact of overweight will be even greater as the representation of nonmucinous, nonrectal cancer will be higher.

In our study, the association between obesity and increased risk of colon cancer was evident for the highest quintile only. Moghaddam and colleagues (4) reported that there is evidence for a dose–response relationship between excess weight and the risk of CRC in both men and women, with some suggestion that the association was stronger for cancer of the colon than for the rectum.

We did not have information about those who emigrated from Israel. However, for this to substantively bias the results, we would have to assume that émigrés who were thin at 17 years were particularly prone to colon cancer, an unlikely occurrence. The absence of data on possible

confounders such as physical activity and dietary composition might affect risk estimates. Case–control studies have shown consistently that high intake of red and processed meats, highly refined grains and starches, and sugars are related to increased risk of CRC (30, 31). The Israeli Center of Disease Control (ICDC) has recently published the results of a national dietary survey (32). They concluded that the adult Jewish population consumes total fat and saturated fat more than the Recommended Daily Allowance (RDA) and fiber less than the RDA (32). Hence, the impact of the Western style diet during adulthood might attenuate the impact of overweight documented during adolescence, unless overweight adolescents adhere to such diets in adulthood to a greater extent than their nonoverweight peers. An association between greater levels of physical activity and decreased risk of colon cancer has been reported (18,33,34), although this remains controversial (35). Hence, increased physical activity among the participants at adulthood might attenuate the impact of overweight at adolescence, again, depending on its distribution by adolescent BMI status.

One of the strengths of our study is the fact that we used measured BMI. Although reported and measured weights correlate well (36–38), it is also known that subjects in the lowest BMI quartile tend to overestimate their weight, whereas subjects in the highest quartile tend to underestimate their weight (36). Hence, these inaccuracies can adversely affect analyses based on reported weight and height.

Campbell and colleagues (7) have showed that reported weight gain of 21+ kg from the age of 20 years was associated with a significantly increased risk of CRC [HR = 1.64 (95% CI, 1.28–2.11)]. We had followed up BMI for only a small fraction of our cohort. In our sample, among adolescents who were not overweight (< 85 th percentile), 60.6% remained so in adulthood (BMI < 25 kg/m²). Hence, the impact of the weight gain among adolescents who were not overweight might have attenuated our HR estimate.

Our results should be viewed in terms of the increasing prevalence of obesity in childhood and adolescence observed in Israel as well as in the United States (17, 39, 40). The prevalence of overweight and obesity in Israel (applying the U.S. CDC BMI ≥ 85 th percentile cutoff point) has increased from 9.9% early in the study period to 16.8% among adolescents in the last decade. There is cause for concern as to the adulthood sequelae of this trend as shown by our results. It is not clear from our findings whether it is overweight and obesity in adolescence that is the culprit or whether adolescent overweight predicts adult obesity (as we have shown) and it is long-term adult obesity which plays a causal role. Whatever the mechanism, it seems that the increasing prevalence of overweight in adolescence will lead to increased rates of colon cancer in adulthood, with an increase in the fraction of adult colon cancer attributable to adolescent overweight. Applying our point estimates to the 32% prevalence of

Table 4. Cox proportional HRs for CRC, according to baseline BMI (<85th or >85th percentile) in 367,478 males born between 1947 and 1966 and followed up through 2006

Cancer (n)	Adjusted HR (95% CI) ^a	P
Colon (390)		
BMI < 85th (328)	1.0 (referent)	<0.001
BMI ≥ 85th (62)	1.75 (1.33–2.3.)	
Rectum (171)		
BMI < 85th (153)	1.0	0.580
BMI ≥ 85th (18)	1.14 (0.70–1.87)	
Colorectal, nonmucinous (476)		
BMI < 85th (417)	1.0	<0.001
BMI ≥ 85th (60)	1.66 (1.29–2.14)	
Colon, nonmucinous (327)		
BMI < 85th (275)	1.0	<0.001
BMI ≥ 85th (52)	1.86 (1.38–2.50)	
Colorectal, mucinous (85)		
BMI < 85th (77)	1.0	0.943
BMI ≥ 85th (8)	1.02 (0.49–2.13)	

^aCox proportional analysis adjusted for year of birth, age at BMI measurement, country of origin, residence (rural or urban), immigration status, socioeconomic status, and height.

excess weight in U.S. adolescents (16) suggests a population fraction in the range of 14.8% for colon cancer attributable to excess adolescent weight in the United States.

In conclusion, in this large cohort, we have shown that overweight in adolescence is associated with a significantly increased risk of colon cancer in adulthood. This should add to the urgency of dealing with this public health hazard in childhood and encourage preventive action.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Z. Levi designed, analyzed, and interpreted the data and drafted the manuscript. J.D. Kark provided the study concept and design, supervised the study, analyzed and interpreted the data, critically revised the manuscript, and obtained funding. M. Barchana and I. Liphshitz conducted the

cancer data linkage. O. Zavdy conducted acquisition of the data. D. Tzav and E. Derazne conducted data management and statistical analysis. M. Furman and B. Gordon provided technical support. Y. Niv critically revised the manuscript. A. Afek and A. Shamiss provided the study concept and design and supervised the study.

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