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Colorectal cancer risk based on extended family history and body mass index

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Abstract

Family history and body mass index (BMI) are well-known risk factors for colorectal cancer (CRC), however their joint effects are not well described. Using linked data for genealogy, self-reported height and weight from driver's licenses, and the Utah SEER cancer registry, we found that an increasing number of first degree relatives (FDR) with CRC is associated with higher standardized incidence ratio (SIR) for overweight/obese probands but not for under/normal weight probands. For probands with two CRC-affected FDRs, the SIR=1.91 (95% CI: 0.52, 4.89) for under/normal weight probands and SIR=4.31 (95% CI: 2.46, 7.00) for overweight/obese probands. In the absence of CRC-affected FDRs, any number of CRC-affected SDRs did not significantly increase CRC risk for under/normal weight probands, but for overweight/obese probands with at least three CRC-affected SDRs the SIR=2.68 (95% CI: 1.29, 4.93). In the absence of CRC-affected FDRs and SDRs, any number of CRC-affected TDRs did not increase risk in under/normal weight probands, but significantly elevated risk for overweight/obese probands with at least two CRC-affected TDRs was observed; SIR=1.32 (95% CI: 1.04, 1.65). For non-syndromic CRC, maximum midlife BMI affects risk based on family history and should be taken into account for CRC risk communication when possible.

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Keywords

colorectal cancer; family history; obesity; UPDB; body mass index; cancer screening

INTRODUCTION

In the U.S. and other developed countries, obesity is recognized as a major public health problem. In 2015–2016, the prevalence of obesity in U.S. adults was 39.8% (Hales, Carroll, Fryar, & Ogden, 2017), rising over the last three decades. Excess body weight, often classified using body mass index (BMI), has been associated with many chronic diseases, including colorectal cancer (CRC) (Ma et al., 2013).

Family history is well-recognized as a strong risk factor for CRC (Andrieu, Launoy, Guillois, Ory-Paoletti, & Gignoux, 2003; Henrikson et al., 2015; Taylor, Burt, Williams, Haug, & Cannon-Albright, 2010). We previously published relative risks (RR) for CRC based on complete CRC family history for the Utah population (Taylor et al., 2010) using a unique resource linking Utah genealogy with statewide cancer registration. These published RRs were estimated for a large number of extended family history constellations, including first to third degree relatives, but did not explore the influence of other factors on risk.

Given the epidemiologic evidence supporting the association of excess body weight and CRC risk (Chan & Giovannucci, 2010), we expanded our previous work to demonstrate the effect of other risk factors in combination with family history of CRC, here presenting initial results for BMI.

METHODS

Utah Population DataBase (UPDB).

The UPDB is a unique population-based resource that includes the genealogy of Utah, from its founders in the mid-1800s to modern day. The UPDB includes data on approximately 11 million individuals, over 3 million of these individuals have at least three (and up to 16) generations of genealogy which links to Utah founders; 1.6 million of these individuals have genealogy which includes at least 12 of 14 immediate ancestors (both parents, all 4 grandparents, and at least 6 of 8 great grandparents). These individuals with complete ancestral genealogy data were used here to ensure adequate and equivalent genealogy data to identify relationships out to third-degree (e.g. first cousins). The individuals in the UPDB are record linked regularly to a number of statewide data resources, including the Utah National Cancer Institute's Surveillance, Epidemiology, and End-Results (SEER) Cancer Registry as well as Utah Driver's License (DL) data.

Utah Cancer Registry.

All independent primary cancers diagnosed or treated in Utah are registered in the Utah Cancer Registry, established in 1966. In 1973 this registry became one of the NCI Surveillance, Epidemiology, and End Results Program (SEER) Cancer registries. Primary site, histology, behavior, stage, grade, and survival data are stored with high levels of follow-

up. In the 1.6 million individuals with ancestral genealogy described above, there were 115,490 individuals with one or more linked cancer diagnoses; 11,680 of these individuals had one or more diagnoses of a primary CRC. CRC cases are defined using SEER codes including International Classification of Diseases – Oncology- Revision 3 primary sites C180–189, C199, C209, C260, and all histologies excluding 9050–9055, 9140, and 9590–9992 (SEER codes 21041–21049, 21051–21052).

Body Mass Index.

New and renewal DL data for Utah drivers have been linked to individual data in the UPDB starting in 1980, with complete data starting in 1999; 814,828 individuals with at least 12/14 immediate ancestors have at least one linked DL record. Each DL record includes self-reported height and weight and date; 343,401 records allow at least one calculated BMI between the age of 35 and 50 years of age (midlife), with BMI for CRC cases measured before diagnosis. BMI was calculated as weight in kilograms divided by height in meters squared. For individuals with more than one linked new or renewal DL record, we used the maximum reported height and weight reported during age 35 to 50 years to represent maximum midlife BMI; this is the BMI measurement referred to in all results. In total, 6,509 of the 11,680 CRC cases with ancestral genealogy have any height and weight linked data, 1,321 CRC cases with ancestral genealogy have midlife BMI data available before diagnosis of CRC.

Estimation of Standardized Incidence Ratios (SIRs).

SIRs were estimated for multiple CRC family history constellations, stratified by BMI categories (under/normal weight or overweight/obese/morbidly obese). Since a well-defined set of individuals were analyzed here and they represent neither the entire UPDB population nor the entire Utah population, it is appropriate to estimate CRC rates only from this (still large) set of individuals who were analyzed here to reduce bias in risk predictions. Rates of CRC for appropriate comparisons were calculated from the 814,828 individuals with both ancestral genealogy and linked DL data in UPDB as follows. All individuals were assigned to one of 132 cohorts defined by sex, 5-year birth year range, and birth state (Utah or not). Cohort-specific CRC rates were estimated as the number of CRC cases in each cohort divided by the number of individuals in the cohort. These rates do not represent Utah CRC rates, but are unbiased rates of CRC for the UPDB population analyzed.

SIRs for CRC for a group of probands (defined by family history and BMI category) were calculated as the ratio of the observed number of CRC cases among the probands to the expected number. The observed number of probands with CRC was counted by cohort. The expected number of CRC cases was estimated by counting all individuals in the group, by cohort, then multiplying the number of individuals in the cohort times the cohort-specific rate of CRC (as described above), and then summing over all cohorts. The SIR is the ratio of the observed to the expected number of probands with CRC for each constellation and BMI category. The distribution of the number of observed CRC cases is assumed to be Poisson with a mean equal to the number of expected CRC cases; 95% confidence intervals were calculated as presented in Agresti (Agresti, 1990).

Relationships.

First-degree relatives (FDR) include parents, siblings, and offspring. Second-degree relatives (SDR) are the first-degree relatives of FDRs and equivalents; they include grandparents, grandchildren, aunts, uncles, nieces, nephews, and half-siblings. Third degree relatives (TDR) are the FDRs of SDRs and equivalent; they include great grandparents, great grandchildren, half-aunts, half-uncles, half-nephews, half-nieces, great aunts, great uncles, and first cousins. BMI data is primarily available since 1999, and cancer data is only available from 1966; therefore, relationships of affected individuals in different generations are less commonly observed than those occurring in the same generation.

University of Utah Institutional Review Board approval was in place for this study.

RESULTS

Table 1 shows the frequency of the probands, and the subset of CRC-affected probands, according to maximum midlife BMI using World Health Organization (WHO) categories. Approximately 63% of individuals analyzed were classified as overweight, obese, or morbidly obese, compared to 71% of the CRC cases.

Table 2 shows estimated SIRs for CRC by presence or absence of FDR family history and for the two BMI-defined subgroups, respectively, ignoring the influence of the other factor. These analyses confirm independent effects of both BMI and family history. Having no family history of CRC is protective for CRC (SIR=0.87, 95% CI: 0.82, 0.92), and having any family history of CRC increases risk (SIR=1.57, 95% CI: 1.35, 1.82). The 130,582 under/normal weight individuals showed a significantly decreased risk for CRC (SIR=0.79, 95% CI: 0.72, 0.87), while the overweight/obese individuals showed no different risk for CRC (SIR=0.99, 95% CI: 0.93, 1.06).

Table 3 shows SIRs based on specific family history constellations that include both close and distant relatives and both BMI categories. When ignoring second- and third-degree relatives, we observed reduced CRC risk for individuals who are under/normal weight who have no first degree family history of CRC (SIR=0.76, 95% CI: 0.68, 0.84); Table 3a. In the overweight/obese category, the estimated CRC risk was significantly elevated in the presence of one and two affected FDRs; overweight/obese individuals with two FDRs had a 4.31-fold higher risk (95% CI: 2.46, 7.00).

Risks were estimated for family history based on affected SDRs in the presence of 0 affected FDRs and ignoring TDRs; Table 3b. Significantly elevated risk was noted for almost all categories of overweight/obese probands with CRC-affected SDRs; SIRs increased from 1.46 (1.03, 2.01) for at least two affected SDRs to 12.20 (1.48, 44.07) for at least five CRC-affected SDRs. No excess risk was observed for any of the family history constellations for under/normal weight probands for any number of CRC-affected SDRs in the absence of no affected FDRs.

Table 3c shows SIR estimates for family history based on affected TDRs in the presence of 0 affected FDRs and 0 affected SDRs. The estimated SIR for individuals with no family

history of CRC out to third-degree (0 FDRs, 0 SDRs, 0 TDRs) is significantly decreased for under/normal weight probands (RR=0.70, 95% CI: 0.60, 0.81) and for overweight/obese probands (SIR=0.73, 95% CI: 0.66, 0.82). In the absence of any first or second-degree CRC-affected relatives, SIRs for CRC in overweight/obese probands were significantly elevated for probands with at least two CRC-affected TDRs (RR=1.32, 95% CI: 1.04, 1.65). No significantly elevated risks for CRC were observed for any TDR family histories for under/normal weight probands.

DISCUSSION

The Utah population database provides a unique opportunity to explore family history and cancer risk. Having previously presented estimates of CRC risk based only on family history, here we evaluated the joint influence of family history and adult obesity, measured via maximum midlife BMI, and confirmed the independent effect of both BMI and family history of CRC on CRC risk (Table 2). These simple comparisons show that a proband's adult BMI has differential effects on CRC risk in the presence of a positive family history of CRC. Specifically, our findings suggest that risk is greater than 2-fold for overweight/obese individuals in the presence of two or more CRC-affected FDRs and three or more CRC-affected SDRs.

The large sample size in the UPDB resource has allowed us to identify sets of probands with specific midlife BMI and family history characteristics and estimate risk for CRC; but many more combinations exist than are shown. Clearly inclusion of other proband characteristics and other risk factors (e.g. proband age or personal history of tobacco use) could further refine estimates of risk. Sample sizes based on the approach taken here would continue to shrink with additional stratification, so a different approach will be necessary. In the future, we will develop and validate models for prediction of cancer that include additional proband characteristics and risk factors. We will use data mining techniques to address issues of interpretability, scalability and unbalance that are inherent in these data.

Andrieu et al 2003 estimated familial RRs in a French sample of 761 pedigrees (Andrieu et al., 2003). They reported slightly higher risks for individuals having a first degree versus a second-degree family history: RR=1.71 (95% CI: 1.35, 2.13) and 1.22 (95% CI: 0.82, 1.76), respectively. They further estimated familial risk at 5.43 (95% CI: 4.28, 6.78) when two family members were affected and 8.52 (95% CI: 5.75, 12.2) when three or more family members were affected. Findings reported by Newcomb *et al* include higher CRC risk with more than one family member with CRC (RR=3.65, 95% CI: 1.81, 7.37) (Newcomb, Taylor, & Trentham-Dietz, 1999).

Current multi-society task force CRC screening guidelines recommend initiating earlier screening colonoscopy in subjects with one or more FDR with CRC (Rex et al., 2017). In short, individuals with two FDRs with CRC or one FDR diagnosed with CRC or an advanced adenoma before age 60 should begin screening at age 40, or 10 years before the youngest related case (Levin et al., 2008; Lieberman et al., 2012; Winawer et al., 2003). This recommendation does not take into account second- or third-degree relatives. Screening is initiated similar to the average risk population irrespective of family history of CRC in the

presence of affected SDR and TDRs. We noted higher CRC risk in overweight/obese individuals with three or more SDRs or two or more TDRs with CRC. Although the number of probands was small in the SDR group, these results may indicate consideration of earlier screening in overweight/obese individuals with multiple SDRs or TDRs with colon cancer.

Obesity is a known risk factor for development of colon cancer, but screening guidelines do not take lifestyle risk factors into account (Chan & Giovannucci, 2010; Ma et al., 2013). Most studies evaluating CRC risk factors do not evaluate the effects of multiple risk factors. Using a large database like UPDB provides a unique advantage for studying potential combined effects of obesity and family history in the development of CRC. To the best of our knowledge, ours is the first study to describe the combined effect of obesity and extended family history of CRC in a proband's CRC risk. Clinically speaking, we believe that this study has implications for risk communication for individuals across the obesity spectrum. This study suggests that maintaining a healthy BMI may in fact mitigate some degree of risk conferred by family history of CRC; that is, until family history includes three or more first or second-degree affected relatives. A 4-fold higher risk of CRC was observed in probands with two or more FDRs who were obese in midlife as compared to a 2-fold higher CRC risk (not significant) in probands with normal weight. Although earlier screening may already be recommended in this cohort (depending on age at relative diagnoses), these findings may indicate that maintaining a normal weight during midlife may reduce the risk of cancer development and potentially mitigate inherited genetic risk. For overweight/obese adults, it may be prudent to query regarding the degree of relationship of CRC-diagnosed relatives. Further studies are needed to evaluate age at diagnosis and whether individuals who have both a strong family history and adult overweight/obesity should be subjected to CRC screening at an earlier age. Promising evidence supports the fact that individuals with a family history are more likely to be adherent to recommended screenings (Henrikson et al., 2015); this may prove beneficial as we move toward personalized or precision prevention and develop more tailored screening recommendations, which could include personal characteristics such as lifetime obesity.

Colon cancer rates are rising in young people (<50 years) and the American Cancer Society now recommends starting screening at age 45 (Wolf et al., 2018). This recommendation however has raised a number of questions regarding resources and achieving overall benefits of colon cancer screening. Decreasing the screening recommendations age from 50 to 45 will roughly add 20 million more individuals in need of screening, adding considerable strain on already limited resources (Anderson & Samadder, 2018). Obesity is suggested as a risk factor in the development of young onset CRC (Kim et al., 2019; Liu et al., 2019). Obesity may also be a limiting factor in obtaining appropriate colon cancer screening. Literature suggests that obese white women are screened less (Fagan, Wender, Myers, & Petrelli, 2011); obese white men also likely undergo reduced screening when compared to subjects with normal BMI (Maruthur, Bolen, Gudzune, Brancati, & Clark, 2012). Consideration of an individual's midlife BMI may be useful in designing personalized screening recommendations in subjects less than age 50 who are obese and also have family history of CRC.

There are several strengths of our study that include the large population size, lack of bias in identification of relatives, and adjudication of all CRC diagnoses from the Utah SEER registry. The UPDB offers the unique opportunity to estimate more nuanced aspects of family history, including first, second and third degree relationships, which is not possible in the majority of epidemiologic studies. Another strength of the study is the availability of DL data (to estimate BMI) in large numbers of individuals.

It is important to note that the Utah population differs from the U.S. population in some important ways. First, the population is relatively homogeneous and largely of Northern European ancestry. The results should not be extrapolated to other populations without validation. The Utah population has been shown to be genetically identical to other populations of Northern European descent, but does differ from the U.S. population in some ways (McLellan, Jorde, & Skolnick, 1984). Utah is ranked at 35 compared to other U.S. states for prevalence of excess body weight from 2001–2004 (Islami, Goding Sauer, Gapstur, & Jemal, 2018). If family history is similarly distributed across the U.S. where obesity rates are higher, risks may differ. Similarly, the state of Utah is lower compared to other states in terms of population attributable fraction (PAF) of incident cancer cases attributable to excess body weight (PAF range=5.9–8.3%), where approximately 6.8% (95% CI: 6.5–7.1) of cancers are attributed to excess body weight.

The SIR estimation approach used has limitations. Some data in the UPDB is censored: genealogy data may be missing or incomplete; some individual or cancer data may not have correctly linked to genealogy data; non-biological familial relationships may be included; and cancers diagnosed before 1966 or outside the state of Utah are not included. The population analyzed consists only of individuals who have received a Utah driver's license during a time period that allows estimation of midlife BMI (35–50 years of age). Decades of studies estimating SIRs for cancer using the UPDB have confirmed that Utah risk estimates based on family history are similar to those reported for other populations. Some family history constellation SIR estimates reported here may have been affected by small sample sizes, yielding wider confidence intervals. We did not account for multiple testing, therefore due to the large number of tests we performed, our results are not as compelling. Finally, SIRs were based only on family history and BMI; additional risk factors such as proband's age and other risk factors were not included and could have affected the risk estimates.

An important limitation to our study is the reliance of BMI obtained from self-report. Weight (and therefore BMI) is likely to be under-estimated. In our previous work, we showed that mean BMI values for the UPDB population were similar to those obtained via the CDC Behavioral Risk Factor Surveillance System (Yates, Johnson, McKee, & Cannon-Albright, 2013). It should also be noted that while self-reported BMI is an imperfect measure of obesity, it offers utility at the population level to investigate associations in large-scale datasets such as UPDB.

Another limitation is in the consideration of CRC as one disease, without an evaluation of different tumor or histopathologic features. Future work focused on the higher risk of adenocarcinomas with mucinous and signet ring-cell histology and poorly differentiated

tumors in younger CRC patients is needed (Ahnen et al., 2014; Murphy et al., 2017) to identify whether family history and obesity are similarly associated with higher risk.

In summary, efforts to integrate more clinical characteristics of the probands; more risk factors (e.g. diet, tobacco exposure), and a more nuanced family history where possible may help to improve efforts for precision cancer prevention. Targeted screening programs for younger adults who are at higher risk due to multiple risk factors may improve early detection and survival. Given the prevalence of a FDR diagnosed with CRC of approximately 3–10% (Henrikson et al., 2015; Taylor et al., 2010) and the growing prevalence of obesity in the U.S. and other developed countries, we hope these results instigate further investigation. This study demonstrates that lifestyle factors such as obesity may further impact CRC risks associated with first and second-degree family history, highlighting the importance of both genetic and lifestyle factors in conferring CRC risk.

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Data Availability Statement. The data that support the findings of this study are available from the Utah Population Database (UPDB) to investigators with appropriate approvals from the Resource for Genetic Epidemiology and the IRB at the University of Utah.

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Table 1.

Maximum midlife BMI distribution of UPDB sample with ancestral genealogy, driver's license data, and colorectal cancer. N (%).

	UPDB with at least 12 of 14 ancestors	
BMI Group	**with DL data**	**with CRC**
Underweight (<18.5 kg/m^2)	4,957 (1.4)	11 (1.0)
Normal (18.5–24.9 kg/m^2)	121,126 (35.3)	374 (28.3)
Overweight (25.0–29.9 kg/m^2)	125,840 (36.7)	507 (38.3)
Obese (30.0–39.9 kg/m^2)	79,428 (23.1)	364 (27.5)
Morbidly obese (>39.9 kg/m^2)	12,050 (3.5)	65 (4.9)
Total	343,401	1,321

Table 2.

Estimated crude CRC standardized incidence ratios by first degree family history and BMI category.

	N	Obs/Exp	SIR (95% CI)	P-value
No first-degree family history	324,986	1143/1321.2	**0.87 (0.82, 0.92)**	**<0.0001**
At least one first-degree relative with CRC	18,415	178/113.5	**1.57 (1.35, 1.82)**	**<0.0001**
BMI<25 kg/m^2 (underweight/normal)	130,582	417/525.6	**0.79 (0.72, 0.87)**	**<0.0001**
BMI≥25 kg/m^2 (overweight/obese)	212,819	904/909.1	0.99 (0.93, 1.06)	0.868

Table 3.

Estimated CRC standardized incidence ratios by BMI category and family history constellation.

	Under/normal weight				Overweight/obese			
Group	**N**	**Obs/Exp**	**SIR (95% CI)**	**P-value**	**N**	**Obs/Exp**	**SIR (95% CI)**	**P-value**
a. First-degree family history of colorectal cancer:								
0/IG/IG	124,001	369/485.7	**0.76 (0.68, 0.84)**	**<0.0001**	**200,985**	**774/835.6**	**0.93 (0.86, 0.99)**	**0.03**
1/IG/IG	6,310	44/37.7	1.17 (0.85, 1.57)	0.33	11,353	113/69.5	**1.63 (1.34, 1.96)**	**<0.0001**
2/IG/IG	256	4/2.1	1.91 (0.52, 4.89)	0.28	444	16/3.7	**4.31 (2.46, 7.00)**	**<0.0001**
≥3/IG/IG	15	0/0.2	-	-	37	1/0.3	2.91 (0.07, 16.20)	0.29
b. Second-degree family history of colorectal cancer:								
0/0/IG	101,806	285/390.1	**0.73 (0.65,0.82)**	**<0.0001**	**163,505**	**579/665.1**	**0.87 (0.80, 0.94)**	**<0.0001**
0/≥1/IG	22,195	84/95.6	0.88 (0.70, 1.09)	0.24	37,480	195/170.4	1.14 (0.99, 1.32)	0.06
0/≥2/IG	2,858	17/14.4	1.18 (0.69, 1.90)	0.51	4,997	38/26.0	**1.46 (1.03, 2.01)**	**0.02**
0/≥3/IG	371	5/2.1	2.37 (0.77, 5.54)	0.06	655	10/3.7	**2.68 (1.29, 4.93)**	**0.01**
0/≥4/IG	55	0/0.3	-	-	74	3/0.5	**5.61 (1.16, 16.39)**	**0.02**
0/≥5/IG	16	0/0.1	-	-	21	2/0.2	**12.20 (1.48, 44.07)**	**<0.0001**
c. Third-degree family history of colorectal cancer:								
0/0/0	67,841	182/260.5	**0.70 (0.60, 0.81)**	**<0.0001**	107,805	322/438.3	**0.73 (0.66, 0.82)**	**<0.0001**
0/0/≥1	33,965	103/129.6	**0.79 (0.65, 0.96)**	**0.02**	55,700	257/226.8	1.13 (1.00, 1.28)	0.05
0/0/≥2	8,501	20/32.2	**0.62 (0.38, 0.96)**	**0.03**	13,934	77/58.3	**1.32 (1.04, 1.65)**	**0.02**
0/0/≥3	1,895	7/7.8	0.90 (0.36, 1.85)	0.86	3,167	17/14.1	1.21 (0.70, 1.94)	0.50