



## Reproductive factors, obesity and risk of colorectal cancer in a cohort of Asian women

Thomas Shing-Hei Wong<sup>a</sup>, Wen Yee Chay<sup>b</sup>, Min-Han Tan<sup>b</sup>, Khuan Yew Chow<sup>c</sup>, Wei-Yen Lim<sup>d,\*</sup>

<sup>a</sup> Saw Swee Hock School of Public Health, National University of Singapore, 12 Science Drive 2, #10-01, 117549, Singapore

<sup>b</sup> National Cancer Centre Singapore, 11 Hospital Drive, 169610, Singapore

<sup>c</sup> National Registry of Diseases Office, Health Promotion Board, 3 Second Hospital Avenue, 168937, Singapore

<sup>d</sup> Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, 308433, Singapore

### ARTICLE INFO

#### Keywords:

Reproductive factors  
Obesity  
Colorectal cancer  
Cohort studies

### ABSTRACT

**Background:** This study evaluated reproductive factors and obesity in relation to colorectal cancer (CRC) in Asian women.

**Methods:** The study cohort comprised 28191 women who were recruited between 1994 and 1997. During 18 years of prospective follow-up, 404 and 212 women developed colon cancer (CC) and rectal cancer (RC) respectively. Cox proportional hazards regression was used.

**Results:** Menstrual factors were not related to the risk of CRC, CC and RC. Gravidity and parity were not associated with CRC or RC, but women who were ever pregnant had a HR of 1.87 (95%CI 1.12–3.14) compared to those never pregnant, and parous women had a HR of 1.79 (95% CI 1.10–2.92) compared to nulliparous women for CC. Use of oral contraceptives and hormone replacement therapy were not associated with CRC, CC or RC.

Compared to women with normal BMI, women who were obese had HRs of 1.39 (95%CI 1.12–1.74) and 1.64 (95%CI 1.24–2.16) for CRC and CC respectively. No increased risk was seen for RC. Adjusted for BMI, for colonic cancer, women in the highest quartile for Waist Circumference had a HR of 2.14 (95%CI 1.42–3.25) compared to the lowest quartile, for Waist Hip Ratio, a HR of 1.74 (95%CI 1.30–2.34), and for Waist-Height ratio, a HR of 1.80 (1.26–2.57). None of these measures were significantly associated with RC.

**Conclusions:** Obesity is positively associated with CC but not RC, and abdominal obesity exerts an independent effect. Reproductive factors had at best a weak effect on CC and RC.

### 1. Introduction

Colorectal cancer (CRC) is the world's second most commonly diagnosed cancer among females after breast cancer [1,2]. It is estimated that a person has a 1 in 8 lifetime probability of developing CRC [3]. Although CRC is not known to have high sensitivity to sex hormones, several lines of evidence have suggested that estrogen may play a role in colorectal tumorigenesis. Estrogen Receptor (ER)  $\alpha$  and  $\beta$  are expressed in both normal colonic tissue and cancerous cells, although ER $\alpha$  is expressed at low levels, and ER $\beta$  is the predominant ER in colonic tissue [4]. The level of expression of ER $\beta$  is significantly lower in cancer cells compared to cells in normal colon tissue, and this decrease is correlated with increasing stage of cancer [5]. The effects of estrogen are multiple and mediated through both genomic and non-genomic pathways [6]. Estrogen can have proliferative, oncogenic and angiogenic effects, and it is these effects that support its role in sex-

hormone dependent cancers such as some breast cancers. However, mouse models of CRC have shown that transfection with ER $\beta$  resulted in cell cycle arrest and inhibition of cell proliferation, with reductions in tumour weight [5]. Clinical trial and observational study data suggest hormone replacement therapy reduces CRC risk [7,8]. Other studies have suggested that oral contraceptives are similarly associated with lowered CRC risk [9,10]. The relationship of other reproductive factors has been inconsistent. For example, parity had an inverse association with CRC risk in some studies (which would be consistent with estrogen as a protective factor) [11–13], but other studies have reported null effects [9,14], or positive associations [15]. These inconsistencies could be due to residual confounding from inadequate adjustment for known risk factors, and differences in populations studied. Further, effect modification by a third factor could also explain these inconsistent results.

Overall, available evidence suggests that high Body-Mass Index is

\* Corresponding author.

E-mail address: [Weiyeen\\_lim@ttsh.com.sg](mailto:Weiyeen_lim@ttsh.com.sg) (W.-Y. Lim).

<https://doi.org/10.1016/j.canep.2018.10.016>

Received 31 July 2018; Received in revised form 29 October 2018; Accepted 31 October 2018

Available online 15 November 2018

1877-7821/ © 2018 Elsevier Ltd. All rights reserved.

associated with higher CRC risk. The increased risk is seen primarily in colonic cancer (CC) rather than rectal cancer (RC). However, gender differences appear to be present, and the evidence for a relationship between BMI and CC in women is less strong [16]. The effect of other measures of adiposity is not well-delineated. Other than BMI, measures such as waist circumference (WC) and Waist Hip Ratio (WHR) correlate better with visceral fat [17]. Although a recent meta-analysis suggests that waist circumference and waist hip ratio were positively associated with both CC and RC [18], a review pointed out that WC and WHR did not appear to add significantly to the association seen between BMI and CRC risk, nor was a statistical interaction observed between BMI and measures of visceral fat in relation to CRC risk [17]. The proposed mechanisms of action involved in obesity include a) hyperinsulinaemia associated with high BMI reduces production of binding proteins Insulin Growth Factor Binding Proteins IGFBP1 and IGFBP2, resultant changes in levels of active Insulin Growth Factor 1 (IGF1) activates Insulin Receptor and IGF1 Receptor signaling, which favour tumour development and spread; b) adipokine changes in relation to obesity causes an increase in leptins (pro-inflammatory, mitogenic and anti-apoptotic) and decrease in adiponectin (anti-inflammatory and sequesters growth factors) shifts the microenvironment to an inflammatory, tumorigenic one; adiposity is also associated with a state of chronic low-grade inflammation, with increases in levels of C-Reactive protein, Interleukin (IL) 1-beta, IL-6 and IL-8; c) sex hormone hypothesis: oestradiol production increases in the presence of adiposity through increased aromatization in peripheral adipose tissue [17].

It is not clear if the sex hormone hypothesis has a significant effect in colorectal carcinogenesis, unlike other cancers with well-known sex hormone sensitivity, as discussed above. Interestingly, a large study of 203,1777 participants in the NIH-AARP Diet and Health Study found effect modification by HRT use on the relationship between measures of obesity and CRC risk, in a complex and unexpected fashion, with inverse association between waist circumference and CRC, and positive association between hip circumference and CRC seen only in HRT users [19].

There hence remains some uncertainty about the effect of obesity and visceral obesity on CRC risk in women. Further, the effect of reproductive factors (as proxies for estrogen exposure) in CRC is still not clear. It is also possible that the relationship between obesity and CRC is modified by estrogen exposure. Finally, it is well known that obesity in Asians differ substantially from other racial groups, and that for equivalent BMI levels, Asians accumulate relatively more visceral fat [20]. This has resulted in alternative BMI cut-offs being recommended for Asian populations [20].

In this study, we evaluated female reproductive factors and measures of obesity, including both BMI and WC, in relation to CRC risk in a cohort of Asian women originally recruited for a breast cancer screening study in Singapore, a multi-ethnic South-East Asian city-state of about 5.5 million people, of which about 74% are Chinese, 13% Malays and 9% Indians.

## 2. Materials and methods

This cohort was established between October 1994 and February 1997 as the Singapore Breast Cancer Screening Project (SBCSP), a population-based randomized controlled trial of mammography screening, described in greater detail in a separate published literature [21]. In summary, the cohort consists of 28,234 women aged between 50 and 64 who participated in mammography screening. Each participant answered a 15-minute long baseline questionnaire administered by a trained interviewer. The questionnaire included questions on ethnicity, highest education level attained, marital status, housing type, occupational status, family history of breast cancer and smoking habits. Reproductive factors elicited included age at menarche, menopausal status, age and type of menopause, pregnancy and delivery history, age at birth of first child and breastfeeding history and duration, and oral

contraceptive use. Height, weight, hip girth and waist circumference of participants were measured by a trained interviewer. In order to reduce error, all measurements (except weight) were performed twice and the average of the two readings was used for analysis.

The SBCSP cohort data was linked with CRC incidence data obtained from the Singapore Cancer Registry (SCR), and mortality information from the Registry of Births & Deaths. The SCR has collected data on all incident cases of cancer in Singapore since 1968. Multiple sources are used, including notifications by the medical profession, pathology records, hospital records, and mortality data from the Registry of Births and Deaths. Since 2007, cancer notifications have been made compulsory under the National Registry of Diseases Act. To ensure data accuracy of at least 95% and inter-rater reliability (Kappa Coefficient) of  $\geq 75\%$ , a separate team of qualified nurses performs an annual audit of cancer cases [22]. Reporting of deaths is mandatory in Singapore.

Incident cases of CC and RC were defined by the *International Classification of Diseases, 9th Edition* (ICD-9) codes 153 and 154 respectively. We excluded those who at baseline reported an age that was less than 50 ( $n = 3$ ). Women who had been diagnosed with CRC prior to the initial screening were also excluded from the cohort ( $n = 40$ ). The resulting cohort consisted of 28,191 women. During the 18 years of follow-up, the number of women who developed CC and RC were 404 and 212 respectively. Follow-up time was defined as the time from recruitment into the SBCSP until date of diagnosis of CRC, date of death or date of censoring, set at 31 December 2012.

For this study, we calculated reproductive period by subtracting age at menarche from age at menopause, and lifetime ovulatory cycles by first subtracting the duration of pregnancies, oral contraceptive use and breastfeeding from the reproductive period and then multiplying that figure by 13. We assumed that each participant woman had 13 menstrual cycles per year with an average cycle length of 28.1 days. Body mass index (BMI) was calculated using weight measured in kilograms divided by the square of the height in metres, and stratified into four categories based on the cut-off points recommended by the World Health Organization (WHO) for Asian populations [20]. The cut-offs were:  $< 18.5 \text{ kg/m}^2$  for underweight,  $18.5 - < 23 \text{ kg/m}^2$  for normal weight,  $23 - < 27.5 \text{ kg/m}^2$  for overweight, and  $27.5 \text{ kg/m}^2$  or greater for obese. Waist-hip ratio (WHR) was calculated by dividing waist circumference over hip girth. A WHR of 0.85 or greater was used as a cut-off for defining abdominal obesity. [23]. Waist-height ratio (WHtR) was calculated by dividing waist circumference over height, and 0.5 or greater was used to define central obesity [24,25]. Further, participants were ranked for these estimates and divided into quartiles.

Standard descriptive statistics were used to summarise the cohort characteristics, including Pearson  $\chi^2$  test for categorical variables, and Student's *t*-test for continuous variables. A Cox proportional hazards regression model was used to estimate the hazard ratios (HRs) and their 95% confidence intervals (CIs) in multivariable analyses. Variables considered *a priori* as important potential confounders were added to the model. These include: age at baseline (continuous), highest education level (no formal education, primary and secondary, tertiary and above), body mass index (continuous), race (Chinese, Malay, Indian, Others), smoking status (non-smoker, ex-smoker, regular smoker). Missing data were coded into a separate "missing" category for adjustment variables. Tests for trend were performed by entering the exposure of interest as a continuous linear term in the model. All *p* values calculated are 2-tailed, and significance was set at  $p < 0.05$ . All analyses were performed using STATA version 11.0 (STATA Corp., Texas, USA) [26]. Written consent was obtained from all participants in the SBCSP, and ethics approval for this study was obtained prior to data linkage and analyses.

## 3. Results

A total of 28,191 women contributed 454,249 person-years of

**Table 1**  
Baseline characteristics of demographic, lifestyle and anthropometric factors in the study population.

Exposure Variables	Colorectal Cancer Cases			Rectal cancer			Subtotal			Non-cases			Total		
	Person-Years	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years	n (%)	Person-Years	n (%)	
<b>I. Demographic and Lifestyle Characteristics</b>															
<b>Marital Status</b>															
Single	75	8 (1.98)	131	13 (6.13)	206	21 (3.41)	19,480	1,186 (4.30)	19,686	1,207 (4.28)			19,686	1,207 (4.28)	
Married	3,412	330 (81.68)	1,582	167 (78.77)	4,994	497 (80.68)	359,548	22,013 (79.83)	364,542	22,510 (79.85)			364,542	22,510 (79.85)	
Others	631	66 (16.34)	260	32 (15.09)	891	98 (15.91)	69,129	4,376 (15.87)	70,021	4,474 (15.87)			70,021	4,474 (15.87)	
<b>Highest Level of Education</b>															
No Formal Education	2,822	274 (67.82)	1,293	139 (65.57)	4,115	413 (67.05)	270,437	16,821 (61.00)	274,552	17,234 (61.13)			274,552	17,234 (61.13)	
Primary and Secondary	1,185	117 (28.96)	585	62 (29.25)	1,770	179 (29.06)	148,885	9,006 (32.66)	150,656	9,185 (32.58)			150,656	9,185 (32.58)	
Tertiary and above	110	13 (3.22)	96	11 (5.19)	206	24 (3.90)	28,835	1,748 (6.34)	29,041	1,772 (6.29)			29,041	1,772 (6.29)	
<b>Race</b>															
Chinese	3,714	367 (90.84)	1,781	190 (89.62)	5,496	557 (90.42)	377,948	23,176 (84.05)	383,444	23,733 (84.19)			383,444	23,733 (84.19)	
Malay	149	14 (3.47)	92	10 (4.72)	241	24 (3.90)	24,711	1,563 (5.67)	24,951	1,587 (5.63)			24,951	1,587 (5.63)	
Indian	102	11 (2.72)	52	5 (2.36)	154	16 (2.60)	22,242	1,382 (5.01)	22,396	1,398 (4.96)			22,396	1,398 (4.96)	
Others	153	12 (2.97)	48	7 (3.30)	201	19 (3.08)	23,257	1,454 (5.27)	23,458	1,473 (5.23)			23,458	1,473 (5.23)	
<b>Housing Type</b>															
HDB (1–3 Rooms)	1,510	150 (37.13)	799	88 (41.51)	2,308	238 (38.64)	174,604	10,751 (38.99)	176,912	10,989 (38.98)			176,912	10,989 (38.98)	
HDB (≥ 4 Rooms)	1,946	188 (46.53)	832	88 (41.51)	2,778	276 (44.81)	205,041	12,654 (45.89)	207,819	12,930 (45.87)			207,819	12,930 (45.87)	
Private Housing	662	66 (16.34)	342	36 (16.98)	1,005	102 (16.56)	68,512	4,170 (15.12)	69,517	4,272 (15.15)			69,517	4,272 (15.15)	
<b>Occupational Status</b>															
Working	1,028	106 (26.24)	670	72 (33.96)	1,698	178 (28.90)	146,036	8,866 (32.15)	147,733	9,044 (32.08)			147,733	9,044 (32.08)	
Unemployed and Retired	114	13 (3.22)	106	11 (5.19)	220	24 (3.90)	18,887	1,149 (4.17)	19,107	1,173 (4.16)			19,107	1,173 (4.16)	
Housewife	2,976	285 (70.54)	1,197	129 (60.85)	4,173	414 (67.21)	283,235	17,560 (63.68)	287,408	17,974 (63.76)			287,408	17,974 (63.76)	
<b>Age at study entry (years)</b>															
< 54	845	87 (21.53)	428	44 (20.75)	1,272	131 (21.27)	138,191	8,287 (30.05)	139,463	8,418 (29.86)			139,463	8,418 (29.86)	
55–59	1,544	143 (35.40)	746	78 (36.79)	2,290	221 (35.88)	168,039	10,308 (37.38)	170,329	10,529 (37.35)			170,329	10,529 (37.35)	
> 60	1,730	174 (43.07)	799	90 (42.45)	2,529	264 (42.86)	141,927	8,980 (32.57)	144,456	9,244 (32.79)			144,456	9,244 (32.79)	
<b>Family History of Breast Cancer</b>															
Yes	123	12 (2.97)	48	5 (2.36)	171	17 (2.76)	11,735	715 (2.59)	11,906	732 (2.60)			11,906	732 (2.60)	
No	3,995	392 (97.03)	1,925	207 (97.64)	5,920	599 (97.24)	436,422	26,860 (97.41)	442,343	27,459 (97.40)			442,343	27,459 (97.40)	
<b>Smoking Status</b>															
Non-smoker	3,738	364 (90.10)	1,882	204 (96.23)	5,620	568 (92.21)	424,931	26,069 (94.54)	430,551	26,637 (94.49)			430,551	26,637 (94.49)	
Ex-smoker	106	9 (2.23)	11	2 (0.94)	117	11 (1.79)	6,728	436 (1.58)	6,844	447 (1.59)			6,844	447 (1.59)	
Regular smoker	274	31 (7.67)	81	6 (2.83)	355	37 (6.01)	16,499	1,070 (3.88)	16,853	1,107 (3.93)			16,853	1,107 (3.93)	
<b>Smoking Intensity (Number of sticks per day)</b>															
0	3,738	364 (90.10)	1,882	204 (96.23)	5,620	568 (92.21)	424,931	26,069 (94.54)	430,551	26,637 (94.49)			430,551	26,637 (94.49)	
1–3	67	7 (1.73)	0	0 (0.00)	67	7 (1.14)	6,276	393 (1.43)	6,343	400 (1.42)			6,343	400 (1.42)	
4–10	231	23 (5.69)	51	5 (2.36)	282	28 (4.55)	12,489	813 (2.95)	12,771	841 (2.98)			12,771	841 (2.98)	
≥ 11	82	10 (2.48)	40	3 (1.42)	122	13 (2.11)	4,462	300 (1.09)	4,584	313 (1.11)			4,584	313 (1.11)	
<b>II. Anthropometric Measurements</b>															
<b>Body Mass Index</b>															
Normal	985	103 (25.50)	669	69 (32.55)	1,654	172 (27.92)	139,760	8,521 (30.9)	141,414	8,693 (30.84)			141,414	8,693 (30.84)	
Underweight	179	17 (4.21)	121	10 (4.72)	300	27 (4.38)	19,942	1,243 (4.51)	20,242	1,270 (4.50)			20,242	1,270 (4.50)	
Overweight	1,760	175 (43.32)	773	85 (40.09)	2,532	260 (42.21)	190,555	11,700 (42.43)	193,088	11,960 (42.42)			193,088	11,960 (42.42)	
Obese	1,194	109 (26.98)	411	48 (22.64)	1,605	157 (25.49)	97,760	6,101 (22.13)	99,365	6,258 (22.20)			99,365	6,258 (22.20)	
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	140	10 (0.04)	140	10 (0.04)			140	10 (0.04)	
<b>Waist Circumference (cm)</b>															
< 74.1	661	66 (16.34)	617	57 (26.89)	1,278	123 (19.97)	114,393	6,946 (25.19)	115,670	7,069 (25.08)			115,670	7,069 (25.08)	
74.1–80.2	936	95 (23.51)	424	46 (21.70)	1,360	141 (22.89)	114,133	6,942 (25.17)	115,493	7,083 (25.13)			115,493	7,083 (25.13)	
80.2–87.1	1,126	114 (28.22)	454	54 (25.47)	1,580	168 (27.27)	111,828	6,910 (25.06)	113,407	7,078 (25.11)			113,407	7,078 (25.11)	
> 87.1	1,395	129 (31.93)	479	55 (25.95)	1,874	184 (29.87)	107,718	6,771 (24.55)	109,591	6,955 (24.67)			109,591	6,955 (24.67)	
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	87	6 (0.03)	87	6 (0.02)			87	6 (0.02)	
<b>Waist-Hip Ratio</b>															

(continued on next page)

**Table 1 (continued)**

Exposure Variables	Colorectal Cancer Cases			Rectal cancer			Subtotal			Non-cases			Total		
	Colon Cancer Person–Years	n (%)	Person–Years	Person–Years	n (%)	Person–Years	Person–Years	n (%)	Person–Years	Person–Years	n (%)	Person–Years	n (%)		
<b>Recommended Cut-Off</b>															
< 0.85	2,574	248 (61.39)	1,403	148 (69.81)	3,977	396 (64.29)	321,675	19,595 (71.06)	325,652	19,991 (70.91)					
> 0.85	1,544	156 (38.61)	570	64 (30.19)	2,115	220 (35.71)	126,345	7,971 (28.91)	128,460	8,191 (29.06)					
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	137	9 (0.03)	137	9 (0.03)					
<b>Quartile</b>															
< 0.77	747	72 (17.82)	542	50 (23.58)	1,289	122 (19.81)	115,611	6,970 (19.81)	116,900	7,092 (25.16)					
0.77–0.81	861	86 (21.29)	480	51 (24.06)	1,341	137 (22.24)	114,477	6,968 (22.24)	115,818	7,105 (25.2)					
0.81–0.86	1,245	115 (28.47)	474	59 (27.83)	1,719	174 (28.25)	109,232	6,756 (28.25)	110,951	6,930 (24.58)					
> 0.86	1,265	131 (32.43)	477	52 (24.53)	1,742	183 (29.71)	108,700	6,872 (29.71)	110,442	7,055 (25.03)					
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	137	9 (0.03)	137	9 (0.03)					
<b>Waist-Height Ratio</b>															
<b>Recommended Cut-Off</b>															
< 0.5	951	98	842	80 (37.74)	1,793	178 (28.90)	161,458	9,788 (35.50)	163,251	9,966 (35.35)					
> 0.5	3,167	306	1,131	132 (62.26)	4,298	438 (71.10)	286,542	17,776 (64.46)	290,840	18,214 (64.61)					
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	157	11 (0.04)	157	11 (0.04)					
<b>Quartile</b>															
< 0.77	682	70	561	53 (25.00)	1,243	123 (19.97)	115,300	6,992 (25.36)	116,543	7,115 (25.24)					
0.77–0.81	943	91	471	48 (22.64)	1,414	139 (22.56)	111,632	6,801 (24.66)	113,046	6,940 (24.62)					
0.82–0.86	1,172	120	412	52 (24.53)	1,584	172 (27.92)	112,410	6,938 (25.16)	113,994	7,110 (25.22)					
> 0.87	1,321	123	529	59 (27.83)	1,850	182 (29.55)	108,658	6,833 (24.78)	110,508	7,015 (24.88)					
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	157	11 (0.04)	157	11 (0.04)					

**Table 2**  
Baseline characteristics of reproductive factors in the study population.

Exposure Variables	Colorectal Cancer Cases			Rectal Cancer			Sub-Total			Non-Cases			Total		
	Colon Cancer Person–Years	n (%)	Person–Years	Rectal Cancer Person–Years	n (%)	Person–Years	Sub-Total Person–Years	n (%)	Person–Years	Non-Cases Person–Years	n (%)	Person–Years	Total Person–Years	n (%)	n (%)
<b>Age at menarche (years)</b>															
< 12	644	62 (15.35)	266	30 (14.15)	910	92 (14.94)	75,817	4,638 (16.82)	76,727	4,730 (16.78)					
13 – 14	1,492	141 (34.90)	731	71 (33.49)	2,224	212 (34.42)	160,803	9,894 (35.88)	163,026	10,106 (35.85)					
15 – 16	1,436	145 (35.89)	666	72 (33.96)	2,102	217 (35.23)	149,259	9,151 (33.39)	151,361	9,412 (33.39)					
> 17	545	56 (13.86)	311	39 (18.40)	856	95 (15.41)	62,098	3,836 (13.91)	62,954	3,931 (13.94)					
Cannot Recall	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	181	12 (0.04)	181	12 (0.04)					
<b>Menopausal Status</b>															
Premenopausal	327	31 (7.67)	181	17 (8.02)	509	48 (7.79)	48,444	2,895 (10.50)	48,953	2,943 (10.44)					
Postmenopausal	3,791	373 (92.33)	1,792	195 (91.98)	5,583	568 (92.21)	3,99,713	24,680 (89.50)	405,296	25,248 (89.56)					
<b>Age at menopause (years)</b>															
< 48	1,368	140 (35.65)	482	55 (25.94)	1,850	195 (31.66)	1,33,477	8,267 (29.98)	1,35,326	8,462 (30.02)					
49 – 50	886	83 (20.54)	454	50 (23.58)	1,340	133 (21.59)	97,793	6,024 (21.85)	99,133	6,157 (21.84)					
51 – 52	506	51 (12.62)	418	40 (18.87)	924	91 (14.77)	77,621	4,756 (17.25)	78,546	4,847 (17.19)					
> 53	1,031	99 (24.50)	438	50 (23.58)	1,469	149 (24.19)	90,315	5,600 (20.31)	91,784	5,749 (20.39)					
Premenopausal	327	31 (7.69)	181	17 (8.03)	509	48 (7.79)	48,444	2,895 (10.50)	48,953	2,943 (10.44)					
Cannot Recall	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	507	33 (0.11)	507	33 (0.12)					
<b>Type of Menopause</b>															
Natural	2,698	266 (65.84)	1,304	141 (66.51)	4,001	407 (66.07)	280,298	17,528 (63.56)	284,299	17,935 (63.62)					
Hysterectomy	484	50 (12.38)	162	20 (9.43)	646	70 (11.36)	49,415	3,059 (11.09)	50,061	3,129 (11.1)					
Premenopausal	327	31 (7.67)	181	17 (8.02)	509	48 (7.79)	48,444	2,895 (10.50)	48,953	2,943 (10.44)					
Cannot Recall	609	57 (14.11)	326	34 (16.04)	935	91 (14.78)	70,000	4,093 (14.85)	70,935	4,184 (14.84)					
<b>Reproductive Period (years)</b>															
< 33	1,272	130 (32.18)	487	55 (25.94)	1,759	185 (30.03)	125,043	7,751 (28.11)	126,802	7,936 (28.15)					
34 – 36	1,017	97 (24.01)	450	49 (23.21)	1,467	146 (23.70)	111,895	6,892 (24.99)	113,361	7,038 (24.97)					
37 – 39	856	85 (21.04)	578	62 (29.15)	1,434	147 (23.86)	106,616	6,548 (23.75)	108,051	6,695 (23.75)					
> 40	646	61 (15.10)	277	29 (13.68)	923	90 (14.61)	55,652	3,456 (12.53)	56,574	3,546 (12.58)					
Premenopausal	327	31 (7.67)	181	17 (8.02)	509	48 (7.80)	48,444	2,895 (10.50)	48,953	2,943 (10.44)					
Unknown	0	0 (0.00)	0	0 (0.00)	0	0 (0.00)	507	33 (0.12)	507	33 (0.12)					
<b>Number of Ovulatory Cycles</b>															
< 319	1,108	107 (26.49)	435	50 (23.58)	1,543	157 (25.49)	97,953	6,135 (22.25)	99,496	6,292 (22.32)					
319 – 386	949	98 (24.26)	380	40 (18.87)	1,329	138 (22.40)	101,558	6,272 (22.75)	1,02,887	6,410 (22.74)					
367 – 437	1,011	96 (23.76)	400	45 (21.23)	1,411	141 (22.89)	99,080	6,087 (22.07)	1,00,491	6,228 (22.09)					
≥ 438	558	57 (14.11)	200	43 (20.28)	958	100 (16.23)	75,372	4,601 (16.69)	76,331	4,701 (16.68)					
Premenopausal	327	31 (7.67)	181	17 (8.02)	509	48 (7.80)	48,444	2,895 (10.50)	48,953	2,943 (10.44)					
Cannot Recall	165	15 (3.71)	176	17 (8.02)	341	32 (5.19)	25,749	1,585 (5.74)	26,090	1,617 (5.74)					
Ever Pregnant	3,968	389 (96.29)	1,774	192 (90.57)	5,760	581 (94.32)	415,276	25,563 (92.70)	421,036	26,144 (92.74)					
Yes	132	15 (3.71)	199	20 (9.43)	331	35 (5.68)	32,881	2,012 (7.30)	33,212	2,047 (7.26)					
No (Nulligravid)	1,206	120 (29.70)	611	67 (31.60)	1,817	187 (30.36)	32,881	9,029 (32.74)	34,699	9,216 (32.69)					
1 – 3	1,849	179 (44.31)	810	83 (39.15)	2,659	262 (42.53)	148,744	11,468 (31.59)	151,404	11,730 (41.61)					
4 – 6	785	75 (18.57)	262	30 (14.15)	1,047	105 (17.05)	186,502	4,061 (14.73)	187,549	4,166 (14.78)					
7 – 9	146	15 (3.71)	90	12 (5.66)	236	27 (4.38)	64,619	1,005 (3.64)	64,855	1,032 (3.66)					
> 10	132	15 (3.71)	199	12 (5.66)	331	35 (5.68)	15,411	2,012 (7.30)	15,742	2,047 (7.26)					
Nulligravid	3,968	387 (95.79)	1,758	190 (89.62)	5,726	577 (93.67)	412,487	25,388 (92.07)	418,213	25,965 (92.1)					
Ever Delivered	150	17 (4.21)	215	22 (10.38)	365	39 (6.33)	35,671	2,187 (7.93)	36,036	2,226 (7.9)					
Yes	156	17 (4.21)	52	6 (2.83)	208	23 (3.73)	25,026	1,525 (5.53)	25,234	1,548 (5.49)					
No (Nulliparous)	609	60 (14.58)	379	43 (20.28)	988	103 (16.72)	74,134	4,485 (16.26)	75,122	4,588 (16.27)					
Number of deliveries	853	82 (20.30)	359	36 (16.98)	1,212	118 (19.16)	96,160	5,855 (21.23)	97,372	5,973 (21.19)					
1	710	72 (17.82)	358	37 (17.45)	1,068	109 (17.69)	77,111	4,738 (17.15)	78,180	4,837 (17.16)					

(continued on next page)

Table 2 (continued)

Exposure Variables	Colorectal Cancer Cases			Rectal Cancer			Sub-Total			Non-Cases			Total		
	Colon Cancer Person–Years	n (%)	Person–Years	Rectal Cancer Person–Years	n (%)	Person–Years	Sub-Total Person–Years	n (%)	Person–Years	n (%)	Person–Years	n (%)	Person–Years	n (%)	
5	596	53 (13.12)	214	214	21 (9.91)	810	74 (12.01)	51,699	3200 (11.60)	52,509	3,274 (11.61)				
6 >	1,044	103 (25.50)	396	396	47 (22.17)	1,440	150 (24.35)	88,356	5595 (20.29)	89,797	5,745 (20.38)				
Nulliparous	150	17 (4.21)	215	215	22 (10.38)	365	39 (6.33)	35,671	2187 (7.93)	36,036	2,226 (7.9)				
<b>Age at first delivery (years)</b>															
< 19	693	69 (17.08)	341	341	38 (17.92)	1,034	107 (17.37)	75,779	4762 (17.27)	76,813	4,869 (17.27)				
20 – 24	1,894	180 (44.55)	783	783	76 (35.85)	2,677	256 (41.56)	167,485	10329 (37.46)	170,161	10,585 (37.55)				
25 – 29	974	94 (23.27)	448	448	56 (26.42)	1,422	150 (24.35)	118,125	7188 (26.07)	119,547	7,338 (26.03)				
> 30	407	44 (10.89)	185	185	20 (9.44)	593	64 (10.39)	50,961	3101 (11.25)	51,554	3,165 (11.23)				
Nulliparous	150	17 (4.21)	215	215	22 (10.38)	365	39 (6.33)	35,671	2187 (7.93)	36,036	2,226 (7.9)				
Cannot Recall	0	0 (0.00)	0	0	0 (0.00)	0	0 (0.00)	137	8 (0.02)	137	8 (0.03)				
<b>History of Breastfeeding</b>															
Yes	2,780	268 (66.34)	1,215	1,215	131 (61.79)	3,994	399 (64.77)	285,394	17,582 (63.76)	289,389	17,981 (63.78)				
No	1,189	119 (29.45)	543	543	59 (27.83)	1,732	178 (28.89)	127,093	7,806 (28.31)	128,825	7,984 (28.32)				
Nulliparous	150	17 (4.21)	215	215	22 (10.38)	365	39 (6.33)	35,671	2,187 (7.93)	36,036	2,226 (7.9)				
<b>Total Duration of breastfeeding (years)</b>															
< 1	1,189	115 (28.47)	446	446	52 (24.53)	1,635	167 (27.11)	1,26,609	7,708 (27.95)	128,243	7,875 (27.93)				
2 – 3	662	64 (15.84)	305	305	29 (13.68)	967	93 (15.10)	64,555	3,991 (14.47)	65,523	4,084 (14.49)				
> 4	834	82 (20.30)	385	385	42 (19.81)	1,219	124 (20.13)	79,955	5,030 (18.24)	81,174	5,154 (18.28)				
Nulliparous	150	17 (4.21)	215	215	22 (10.38)	365	39 (6.33)	35,671	2,187 (7.93)	36,036	2,226 (7.9)				
Does not breastfeed	1,189	119 (29.45)	543	543	59 (27.83)	1,732	178 (28.89)	127,093	7,806 (28.31)	128,825	7,984 (28.32)				
Cannot Recall	95	7 (1.74)	78	78	8 (3.77)	174	15 (2.43)	14,276	853 (3.10)	14,450	868 (3.08)				
<b>Use of OC</b>															
Yes	1,441	139 (34.41)	694	694	78 (36.79)	2,135	217 (35.23)	171,244	10,487 (38.03)	173,379	10,704 (37.97)				
No	2,677	265 (65.59)	1,279	1,279	134 (63.21)	3,956	399 (64.77)	276,914	17,088 (61.97)	280,870	17,487 (62.03)				
<b>Age started using OC</b>															
< 24	184	17 (4.21)	137	137	12 (5.66)	321	29 (4.71)	25,360	1,542 (5.59)	25,681	1,571 (5.57)				
25–29	549	52 (12.87)	283	283	32 (15.09)	832	84 (13.64)	70,660	4,307 (15.62)	71,492	4,391 (15.58)				
30–34	532	52 (12.87)	174	174	22 (10.38)	706	74 (12.01)	55,156	3,385 (12.28)	55,862	3,459 (12.27)				
> 35	175	18 (4.46)	101	101	12 (5.66)	276	30 (4.87)	20,069	1,253 (4.54)	20,345	1,283 (4.55)				
No OC	2,677	265 (65.59)	1,279	1,279	134 (63.21)	3,956	399 (64.77)	276,914	17,088 (61.97)	280,870	17,487 (62.03)				
<b>Duration of using OC (years)</b>															
< 2	784	78 (19.31)	379	379	43 (20.28)	1,163	121 (19.64)	95,154	5,823 (21.12)	96,317	5,944 (21.08)				
> 2	645	60 (14.85)	315	315	35 (16.51)	960	95 (15.42)	75,804	4,647 (16.85)	76,765	4,742 (16.82)				
Unknown	12	1 (0.25)	0	0	0 (0.00)	12	1 (0.17)	285	17 (0.06)	297	18 (0.06)				
No OC	2,677	265 (65.59)	1,279	1,279	134 (63.21)	3,956	399 (64.77)	276,914	17,088 (61.97)	280,870	17,487 (62.03)				
<b>Use of HRT</b>															
Yes	523	50 (12.38)	171	171	22 (10.38)	695	72 (11.69)	61,031	3,681 (13.35)	61,725	3,753 (13.31)				
No	3,595	354 (87.62)	1,802	1,802	190 (89.62)	5,397	544 (88.31)	387,127	23,894 (86.65)	392,523	24,438 (86.69)				
<b>Duration of using HRT (years)</b>															
< 1	236	20 (4.95)	56	56	7 (3.30)	292	27 (4.38)	26,920	1,621 (5.88)	27,212	1,648 (5.85)				
> 1	287	30 (7.43)	116	116	15 (7.08)	403	45 (7.31)	34,110	2,060 (7.47)	34,513	2,105 (7.47)				
No HRT	3,595	354 (87.62)	1,802	1,802	190 (89.62)	5,397	544 (88.31)	387,127	23,894 (86.65)	392,523	24,438 (86.69)				

follow-up time. 616 of these women were subsequently diagnosed with CRC - 404 had colonic cancer and 212 had RC. Baseline characteristics for all study participants are presented in Table 1. During the period under study, the incidence rate of CRC was 135.61 per 100,000 person-years. The proportion of Chinese was higher among CRC cases (90.42%) compared to non-cases (84.05%). CRC cases also had a higher percentage of women with no formal education (67.05% versus 61.00%) and a higher average age (59.04 versus 57.89 years). The proportion of non-smokers was higher among non-cases (94.54%) compared to cases (92.21%). Among ex-smokers and regular smokers, the average number of cigarettes smoked per day was higher among cases (10.33) than non-cases (9.23). The difference between CRC cases and non-cases was not statistically different for BMI. Compared to non-cases, CRC cases had a higher waist circumference (82.56 cm versus 81.07 cm), a higher waist-hip ratio (0.83 versus 0.82) and a higher waist-height ratio (0.36 versus 0.35).

Table 2 summarises baseline reproductive factors. 89.56% of the study population were postmenopausal, and the majority had natural menopause rather than surgically or chemically induced ones. Slightly more than one-third (37.97%) used Oral Contraceptives (OC), while 13.31% reported ever using Hormone Replacement Therapy (HRT). 92.74% of the population were pregnant before and 92.1% had delivered at least 1 child. CRC cases in this study were found to have a higher average number of pregnancies (4.65 versus 4.33) and higher number of deliveries (4.27 versus 4.06).

Table 3 shows the association of several reproductive variables on the risk of CRC, CC and RC. Menstrual factors such as age at menarche, status and age at menopause, reproductive years and number of ovulatory cycles were not associated with CRC, CC and RC. Gravidity and parity were not associated with CRC or RC, but women who were ever pregnant had a HR of 1.87 (95%CI 1.12–3.14) compared to those never pregnant, and parous women had a HR of 1.79 (95% CI 1.10–2.92) compared to nulliparous women for CC. For every unit increase in pregnancy, the risk of having CC increased by 4% (95% CI: 1.00–1.09;  $p$ -value = 0.04), while every additional delivery increased CC risk by a similar amount. Examination of the data suggests a possible threshold at 2 or more deliveries, as the HRs for 2,3,4,5 and 6 or more are relatively similar. The number of miscarriages, age at first and last delivery, as well as breastfeeding history and duration were not associated with risk of CRC, CC and RC. No relationship was observed between CRC and the use of exogenous reproductive hormones such as oral contraceptives (OC) and hormone replacement therapy (HRT).

Table 4 shows the association of measures of obesity with CRC, CC and RC. Compared to women with normal BMI, women who were obese had HRs of 1.39 (95%CI 1.12–1.74) and 1.64 (95%CI 1.24–2.16) for CRC and CC respectively. Adjusted for BMI, women in the highest quartile for Waist Circumference had HRs of 1.62 (95%CI 1.17–2.25) and 2.14 (95%CI 1.42–3.25) for CRC and CC respectively compared to the lowest quartile, for Waist Hip Ratio (WHR), HRs of 1.44 (1.14–1.83) and 1.74 (95%CI 1.30–2.34) for CRC and CC respectively, and for Waist-Height Ratio (WHtR), HRs of 1.57 (1.13–2.17) and 1.80 (1.26–2.57) respectively for CRC and CC. Using a cut-off of  $> 0.85$ , women with a high WHR had 1.33 (95%CI 1.12–1.57) and 1.50 (1.22–1.84) the hazards of CRC and CC respectively compared to women with normal WHR, while women with high WHtR ( $> 0.5$ ) had HRs of 1.30 (95% CI 1.07–1.57) and 1.66 (95%CI 1.30–2.12) for CRC and CC respectively. Every 1 cm increase in waist circumference was associated with a 2% and 3% increase in risk for CRC and CC respectively. None of these measures of abdominal obesity were significantly associated with RC.

#### 4. Discussion

In this study, we find that reproductive factors and breastfeeding do not appear to be significant risk factors of CRC, CC and RC. Similar to many studies, we show that high BMI using Asian-specific cut-offs is

associated with increased risk of CRC, and specifically of CC, but not RC. We further find that measures of abdominal obesity are independently associated with CRC and CC, but not RC.

Investigations into the relationship between reproductive factors and CRC risk have centred on the role of estrogen exposure as a possible protective factor. We did not find a protective effect of HRT or OC use, and a longer reproductive period was also not protective. In contrast, we found that parity and gravidity were associated with increased risk of CC (but not RC). No clear dose-response relationship was seen.

Our results for HRT and OC are not consistent with results from other prospective cohort studies [7–10]. It should be noted that only about 12–13% of our study population ever used HRT, and about one-third used OC. Further, studies of HRT and OC are complicated by different formulations of these compounds over time and in different countries.

Some prospective studies, including Women's Health Initiative (WHI) observational study [12] and NIH-AARP [13], have reported protective effects of parity on CC, suggesting that oestrone, the major estrogen form in pregnancy may be the causative agent as it has anti-proliferative effects. Our results are not consistent with these findings. In the WHI study, parity was borderline protective, but there was no dose-response effect, although similar hazard ratios were seen at 2, 3 or 4 or more children leading the authors to suggest the presence of a threshold effect. Having 2 or more children was protective with a HR of 0.8 compared to nulliparous women in their study. (Similarly, no dose-response effect as seen for OC use.) It should be noted however, that it is not clear that oestrone is protective as a study from the New York University Women's Health Study reported that oestrone levels were positively associated with CRC risk [27].

Early age at menarche and late age at menopause were associated with higher CRC risk in both the WHI and NIH-AARP studies, and early age at menarche in a Japanese cohort study [24]; these results suggest that a longer reproductive period (and hence higher estrogen exposure) increases CRC risk. In contrast, we find that age at menarche, age at menopause, total reproductive period and estimated ovulatory cycles were all not associated with CRC. A meta-analysis of 22 observation studies suggested that age at menarche was not associated with risk of CRC [28]. The effect of age at menopause has also been difficult to tease out. Null findings were reported in the Japanese cohort [14] and other studies [29,30], including one that used Mendelian randomization to reduce confounding, consistent with our results, but in contrast to the studies described above.

Explanations for these differences include: differences in study populations, differing formulations of HRT and OC, and the possibility of unmeasured confounding. For example, Asian populations (including ours) consume soy products at a much higher frequency than in non-Asian populations, and phytoestrogens in soy products are postulated to have estrogenic effects at the cellular level.

Similar to the majority of published studies and several published meta-analyses [31–33], we find a positive association between BMI and CRC, and with a much stronger effect on CC than RC (in our case, BMI was not associated with RC risk). Larsson et al [31] in a meta-analysis of 31 studies, estimated a 12% increased risk of CC (95% CI: 1.07–1.18) for every 5 kg m<sup>-2</sup> increase in women while RC was shown to be statistically insignificant (RR: 1.03; 95% CI: 0.99–1.08), similar to our findings. It should be noted that in our study, we used Asian-specific cut-offs, which used lower BMI levels for cut-offs.

Unlike BMI, the association between central obesity (as measured by indicators such as WC, WHR and WHtR) has not been as consistent. A recent systematic review suggests that measures of abdominal obesity did not add significantly to risk estimates above that provided by BMI [17]. Our study however suggests that abdominal obesity is independently important beyond BMI, and indeed all 3 measures of abdominal obesity (WC, WHR and WHtR) were positively associated with CRC risk after adjustment with BMI, in a strong dose-response fashion. This increased risk was seen entirely in CC but not RC. A large

**Table 3**  
Crude and multivariate adjusted HRs and 95% confidence intervals for reproductive-related exposure variables and risk of colorectal, colon and rectal cancer.

Exposure Variable	Colorectal Cancer			Colon Cancer		Rectal Cancer	
	Number of Cases	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>
<b>Age at menarche (years)</b>							
Continuous		1.05 (1.01 – 1.09)	0.99 (0.94 – 1.03)	1.03 (0.98 – 1.09)	0.97 (0.91 – 1.02)	1.07 (1.00 – 1.15)	1.02 (0.96 – 1.10)
< 12	92	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
13 – 14	212	1.09 (0.85 – 1.39)	0.95 (0.74 – 1.21)	1.07 (0.80 – 1.45)	0.92 (0.68 – 1.24)	1.11 (0.73 – 1.71)	1.01 (0.65 – 1.55)
15 – 16	217	1.20 (0.94 – 1.53)	0.92 (0.74 – 1.21)	1.19 (0.88 – 1.60)	0.89 (0.65 – 1.21)	1.22 (0.80 – 1.86)	0.99 (0.64 – 1.55)
> 17	95	1.26 (0.95 – 1.68)	0.86 (0.64 – 1.16)	1.11 (0.77 – 1.59)	0.72 (0.49 – 1.05)	1.59 (0.99 – 2.56)	1.18 (0.71 – 1.95)
<i>P</i> <sub>trend</sub>		0.06	0.34	0.36	0.11	0.05	0.57
<b>Menopausal Status</b>							
Premenopausal	48	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Postmenopausal	568	1.45 (1.07 – 1.94)	0.97 (0.71 – 1.34)	1.48 (1.02 – 2.13)	0.97 (0.65 – 1.43)	1.39 (0.85 – 2.29)	0.99 (0.58 – 1.68)
<b>Age at menopause (years)<sup>2</sup></b>							
Continuous		1.01 (0.99 – 1.03)	1.01 (0.99 – 1.02)	0.99 (0.97 – 1.02)	0.99 (0.97 – 1.01)	1.04 (1.00 – 1.07)	1.04 (1.00 – 1.07)
< 48	195	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
49 – 50	133	0.93 (0.75 – 1.16)	0.93 (0.74 – 1.17)	0.81 (0.62 – 1.06)	0.81 (0.61 – 1.07)	1.24 (0.85 – 1.82)	1.27 (0.84 – 1.92)
51 – 52	91	0.80 (0.62 – 1.03)	0.79 (0.61 – 1.03)	0.62 (0.45 – 0.86)	0.63 (0.45 – 0.87)	1.25 (0.83 – 1.88)	1.26 (0.81 – 1.96)
> 53	149	1.13 (0.91 – 1.40)	1.08 (0.86 – 1.34)	1.04 (0.81 – 1.35)	0.97 (0.75 – 1.27)	1.34 (0.91 – 1.97)	1.37 (0.92 – 2.06)
<i>P</i> <sub>trend</sub>		0.56	0.82	0.73	0.45	0.14	0.14
<b>Type of Menopause</b>							
Natural	407	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Hysterectomy	70	0.97 (0.76 – 1.26)	1.03 (0.80 – 1.33)	1.06 (0.79 – 1.44)	1.14 (0.84 – 1.55)	0.80 (0.50 – 1.29)	0.80 (0.50 – 1.29)
<b>Reproductive Period (Years)</b>							
Continuous		1.00 (0.93 – 1.02)	1.00 (0.99 – 1.02)	0.99 (0.97 – 1.01)	1.00 (0.97 – 1.02)	1.02 (0.99 – 1.05)	1.02 (0.99 – 1.06)
< 33	185	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
34 – 36	146	0.88 (0.71 – 1.09)	0.91 (0.73 – 1.13)	0.83 (0.64 – 1.08)	0.86 (0.66 – 1.12)	1.00 (0.67 – 1.46)	1.01 (0.69 – 1.48)
37 – 39	147	0.93 (0.75 – 1.15)	1.00 (0.80 – 1.24)	0.76 (0.58 – 1.00)	0.83 (0.63 – 1.10)	1.32 (0.92 – 1.90)	1.39 (0.96 – 2.00)
> 40	90	1.09 (0.85 – 1.40)	1.12 (0.87 – 1.44)	1.05 (0.78 – 1.43)	1.09 (0.80 – 1.48)	1.18 (0.75 – 1.85)	1.18 (0.75 – 1.85)
<i>P</i> <sub>trend</sub>		0.71	0.42	0.61	0.96	0.18	0.15
<b>Ovulatory Cycle</b>							
Continuous		1.00 (0.99 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)
< 318	157	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
319 – 385	138	0.85 (0.67 – 1.06)	0.89 (0.70 – 1.12)	0.88 (0.67 – 1.16)	0.93 (0.70 – 1.23)	0.77 (0.51 – 1.17)	0.80 (0.52 – 1.21)
386 – 437	141	0.88 (0.70 – 1.11)	0.97 (0.76 – 1.22)	0.88 (0.67 – 1.16)	0.97 (0.73 – 1.29)	0.89 (0.59 – 1.33)	0.95 (0.63 – 1.43)
> 438	100	0.82 (0.64 – 1.06)	0.93 (0.72 – 1.21)	0.69 (0.50 – 0.95)	0.79 (0.57 – 1.10)	1.12 (0.74 – 1.68)	1.23 (0.80 – 1.89)
<i>P</i> <sub>trend</sub>		0.17	0.75	0.03	0.26	0.55	0.31
<b>Ever Pregnant</b>							
Yes	581	1.31 (0.93 – 1.85)	1.21 (0.86 – 1.70)	2.05 (1.23 – 3.44)	1.87 (1.12 – 3.14)	0.76 (0.47 – 1.20)	0.71 (0.45 – 1.13)
No (Nulligravid)	35	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>Number of pregnancies</b>							
Continuous		1.06 (1.02 – 1.09)	1.02 (0.99 – 1.05)	1.08 (1.04 – 1.12)	1.04 (1.00 – 1.09)	1.01 (0.95 – 1.06)	0.97 (0.92 – 1.03)
Nulligravid	35	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1 – 3	187	1.18 (0.82 – 1.69)	1.20 (0.84 – 1.73)	1.76 (1.03 – 3.01)	1.80 (1.05 – 3.09)	0.74 (0.45 – 1.22)	0.75 (0.46 – 1.24)
4 – 6	262	1.32 (0.93 – 1.88)	1.21 (0.85 – 1.73)	2.10 (1.24 – 3.56)	1.92 (1.13 – 3.27)	0.73 (0.45 – 1.19)	0.68 (0.41 – 1.12)
7 – 9	105	1.53 (1.05 – 2.25)	1.21 (0.81 – 1.79)	2.56 (1.47 – 4.46)	1.98 (1.13 – 3.49)	0.76 (0.43 – 1.34)	0.62 (0.34 – 1.12)
> 10	27	1.67 (1.01 – 2.77)	1.22 (0.72 – 2.04)	2.18 (1.07 – 4.46)	1.55 (0.74 – 3.22)	1.29 (0.63 – 2.64)	0.99 (0.47 – 2.09)
<i>P</i> <sub>trend</sub>		< 0.01	0.54	< 0.01	0.17	0.79	0.40
<b>Ever Delivered</b>							
Yes	577	1.28 (0.92 – 1.77)	1.17 (0.84 – 1.62)	1.97 (1.21 – 3.20)	1.79 (1.10 – 2.92)	0.75 (0.48 – 1.16)	0.70 (0.44 – 1.09)
No (Nulliparous)	39	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>Number of deliveries</b>							
Continuous		1.06 (1.03 – 1.10)	1.02 (0.98 – 1.06)	1.08 (1.04 – 1.13)	1.04 (0.99 – 1.09)	1.02 (0.96 – 1.08)	0.98 (0.92 – 1.04)
Nulliparous	39	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	23	0.84 (0.50 – 1.41)	0.83 (0.50 – 1.39)	1.42 (0.73 – 2.79)	1.41 (0.72 – 2.76)	0.39 (0.16 – 0.96)	0.39 (0.16 – 0.95)
2	103	1.26 (0.87 – 1.83)	1.32 (0.91 – 1.91)	1.69 (0.99 – 2.89)	1.76 (1.03 – 3.02)	0.94 (0.56 – 1.57)	0.98 (0.58 – 1.64)
3	118	1.12 (0.78 – 1.61)	1.12 (0.78 – 1.62)	1.78 (1.06 – 3.01)	1.80 (1.06 – 3.03)	0.61 (0.36 – 1.03)	0.61 (0.36 – 1.04)
4	109	1.29 (0.90 – 1.86)	1.18 (0.82 – 1.71)	1.96 (1.15 – 3.32)	1.79 (1.05 – 3.06)	0.78 (0.46 – 1.32)	0.71 (0.42 – 1.22)
5	74	1.31 (0.89 – 1.93)	1.13 (0.76 – 1.67)	2.15 (1.25 – 3.72)	1.85 (1.07 – 3.22)	0.66 (0.36 – 1.19)	0.57 (0.31 – 1.05)
6 >	150	1.56 (1.10 – 2.22)	1.22 (0.84 – 1.76)	2.47 (1.48 – 4.12)	1.92 (1.13 – 3.26)	0.86 (0.52 – 1.43)	0.67 (0.39 – 1.15)
<i>P</i> <sub>trend</sub>		< 0.01	0.34	< 0.01	0.03	0.93	0.20
<b>Number of miscarriage / abortion</b>							
Continuous		1.04 (0.96 – 1.13)	1.02 (0.94 – 1.11)	1.08 (0.98 – 1.18)	1.05 (0.96 – 1.16)	0.97 (0.83 – 1.13)	0.96 (0.82 – 1.12)
0	345	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
1	134	0.92 (0.76 – 1.13)	0.91 (0.75 – 1.11)	0.96 (0.75 – 1.22)	0.95 (0.74 – 1.21)	0.85 (0.60 – 1.21)	0.85 (0.60 – 1.21)
2	63	1.07 (0.81 – 1.39)	1.03 (0.79 – 1.35)	0.97 (0.69 – 1.37)	0.93 (0.66 – 1.32)	1.25 (0.81 – 1.92)	1.22 (0.79 – 1.88)
> 3	36	1.27 (0.90 – 1.78)	1.16 (0.82 – 1.64)	1.60 (1.09 – 2.34)	1.44 (0.98 – 2.10)	0.62 (0.27 – 1.41)	0.59 (0.26 – 1.35)
<i>P</i> <sub>trend</sub>		0.36	0.67	0.16	0.36	0.69	0.59
<b>Age at first delivery (years)</b>							
Continuous		0.99 (0.97 – 1.01)	1.00 (0.98 – 1.02)	0.99 (0.97 – 1.01)	1.00 (0.98 – 1.03)	0.99 (0.96 – 1.02)	1.00 (0.96 – 1.03)
< 19	107	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
20 – 24	256	1.07 (0.86 – 1.35)	1.03 (0.81 – 1.30)	1.17 (0.89 – 1.55)	1.13 (0.84 – 1.51)	0.90 (0.61 – 1.33)	0.84 (0.56 – 1.26)
25 – 29	150	0.89 (0.70 – 1.14)	0.95 (0.72 – 1.27)	0.86 (0.63 – 1.18)	0.95 (0.67 – 1.35)	0.94 (0.62 – 1.42)	0.95 (0.59 – 1.52)
> 30	64	0.88 (0.65 – 1.20)	0.95 (0.66 – 1.36)	0.94 (0.64 – 1.37)	1.05 (0.68 – 1.62)	0.78 (0.45 – 1.34)	0.77 (0.42 – 1.44)
<i>P</i> <sub>trend</sub>		0.15	0.63	0.19	0.80	0.50	0.63

(continued on next page)

Table 3 (continued)

Exposure Variable	Colorectal Cancer			Colon Cancer		Rectal Cancer	
	Number of Cases	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>
<b>History of Breastfeeding<sup>2</sup></b>							
Yes	399	1.00 (0.84 – 1.19)	0.96 (0.80 – 1.15)	1.00 (0.81 – 1.25)	0.95 (0.76 – 1.19)	0.99 (0.73 – 1.35)	0.96 (0.70 – 1.31)
No	178	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>Total Duration of Breastfeeding (years)<sup>2</sup></b>							
Continuous		1.00 (0.98 – 1.03)	0.99 (0.96 – 1.02)	1.00 (0.97 – 1.03)	0.98 (0.95 – 1.02)	1.01 (0.97 – 1.06)	1.00 (0.95 – 1.05)
No Breastfeeding	178	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
< 1	167	0.94 (0.76 – 1.17)	0.94 (0.76 – 1.17)	0.97 (0.75 – 1.26)	0.98 (0.75 – 1.26)	0.88 (0.61 – 1.28)	0.88 (0.60 – 1.28)
2 – 3	93	1.03 (0.80 – 1.33)	0.98 (0.76 – 1.26)	1.07 (0.79 – 1.45)	1.01 (0.74 – 1.37)	0.97 (0.62 – 1.51)	0.92 (0.58 – 1.45)
> 4	124	1.12 (0.89 – 1.41)	1.00 (0.78 – 1.28)	1.11 (0.84 – 1.48)	0.99 (0.73 – 1.34)	1.13 (0.76 – 1.68)	1.02 (0.66 – 1.57)
	<i>P</i> <sub>trend</sub>	0.29	0.99	0.39	0.98	0.52	0.95
<b>Use of OC</b>							
Yes	217	0.88 (0.75 – 1.04)	0.95 (0.81 – 1.13)	0.85 (0.69 – 1.04)	0.92 (0.75 – 1.14)	0.94 (0.71 – 1.25)	1.01 (0.76 – 1.35)
No	399	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>Age started using OC (years)</b>							
Continuous		1.02 (0.99 – 1.05)	0.99 (0.96 – 1.03)	1.03 (0.99 – 1.06)	1.00 (0.96 – 1.04)	1.01 (0.96 – 1.06)	0.98 (0.93 – 1.04)
< 24	29	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
25–29	84	1.04 (0.68 – 1.59)	0.97 (0.63 – 1.48)	1.10 (0.64 – 1.90)	1.04 (0.60 – 1.79)	0.96 (0.49 – 1.86)	0.88 (0.45 – 1.71)
30–34	74	1.18 (0.77 – 1.81)	0.95 (0.61 – 1.47)	1.41 (0.82 – 2.42)	1.13 (0.64 – 2.00)	0.84 (0.42 – 1.70)	0.68 (0.33 – 1.40)
> 35	30	1.32 (0.79 – 2.19)	0.94 (0.55 – 1.62)	1.35 (0.70 – 2.62)	0.95 (0.47 – 1.90)	1.27 (0.57 – 2.82)	0.94 (0.40 – 2.22)
	<i>P</i> <sub>trend</sub>	0.20	0.80	0.16	0.95	0.78	0.61
<b>Duration of using OC (years)</b>							
Continuous		1.00 (0.99 – 1.01)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)
No OC	399	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
< 2	121	0.88 (0.72 – 1.08)	0.96 (0.78 – 1.19)	0.85 (0.66 – 1.10)	0.94 (0.73 – 1.21)	0.94 (0.66 – 1.32)	1.01 (0.72 – 1.44)
> 2	95	0.87 (0.69 – 1.09)	0.93 (0.74 – 1.17)	0.82 (0.62 – 1.09)	0.89 (0.67 – 1.18)	0.96 (0.66 – 1.39)	1.02 (0.70 – 1.49)
	<i>P</i> <sub>trend</sub>	0.14	0.51	0.11	0.38	0.74	0.90
<b>Use of HRT</b>							
Yes	72	0.84 (0.65 – 1.07)	0.98 (0.76 – 1.26)	0.89 (0.66 – 1.20)	1.08 (0.79 – 1.47)	0.73 (0.47 – 1.41)	0.81 (0.51 – 1.28)
No	544	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>Duration of using HRT (years)</b>							
Continuous		1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (0.99 – 1.00)	1.00 (0.99 – 1.00)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)
No HRT	544	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
< 1	27	0.71 (0.48 – 1.05)	0.82 (0.56 – 1.21)	0.81 (0.51 – 1.27)	0.96 (0.61 – 1.51)	0.53 (0.25 – 1.13)	0.58 (0.27 – 1.25)
> 1	45	0.94 (0.69 – 1.27)	1.11 (0.82 – 1.52)	0.96 (0.66 – 1.39)	1.18 (0.80 – 1.73)	0.90 (0.53 – 1.51)	0.99 (0.58 – 1.71)
	<i>P</i> <sub>trend</sub>	0.31	0.79	0.59	0.49	0.33	0.62

<sup>1</sup> Adjusted for age at baseline (continuous), housing type (HDB [1–3 rooms], HDB [ $\geq$  4 rooms], private housing), body mass index (continuous), race (Chinese, Malay, Indian, Others).

<sup>2</sup> Additionally adjusted for number of pregnancies and age at first delivery.

prospective study in Europe reported that waist-circumference and waist-hip ratio were associated with CC but not RC [34], similar to our study, as did a prospective study in China [35]. A pooled analysis of older adults in Europe reported abdominal obesity measures were significantly associated with CRC [36], while a prospective study conducted in the United States [37] showed central obesity was associated with CC. This last study, using the Framingham cohort, suggested that waist circumference was a more significant predictor than BMI.

Overall, our results showing a null association of reproductive factors with CRC might indicate that the sex hormone hypothesis is a less likely explanation for the role of obesity in CRC. The positive association of abdominal obesity with CRC may provide support for the theory that adipokines and subclinical chronic inflammation (both of which are mediated by visceral fat) play a role in colonic carcinogenesis.

The major strengths of our study are its large sample size and long duration of follow-up of this cohort. The comprehensive system of the cancer registration in Singapore and the standardized case confirmation procedure ensured that only incident colorectal cases were included in this study. Further measurements of height, weight and measures of abdominal obesity were performed by trained interviewers, and not from self-reports.

Limitations of our study include self-reporting of reproductive variables, which could not be verified with clinical or administrative records. In addition, additional relevant information such as family history of colorectal cancer and use of fertility treatments were also not ascertained. Further, women in this cohort lived through a period of major changes in lifestyle as Singapore transitioned from a less

developed economy into a developed one, with significant social changes related to lifestyle such as reductions in physical activity and changes in diet. As dietary history and physical activity were not captured in this study, confounding from these factors are possible.

Finally, false positives due to testing of multiple exposures with the outcome of interest, and false negatives due to insufficient power as a consequence of multiple variable adjustments could have occurred. We believe that the former is less likely as the positive associations we found appear to be consistent and internally coherent (for example, the positive association of BMI as a continuous measure, and as a categorical variable). The latter could have occurred in particular for RC, as the numbers of RC cases is relatively low, and some confidence intervals were very wide.

In conclusion, our study shows that obesity is positively related to CC but not RC risk. In addition, abdominal obesity appears to exert an independent effect. Reproductive factors in contrast were not associated with CC or RC, and only parity and gravidity were found to be risk-conferring.

#### Authorship contribution

Wen Yee Chay, Min-Han Tan and Wei-Yen Lim planned and devised this study. Wen Yee Chay is currently the Principal Investigator of the Singapore Breast Cancer Screening Project cohort study. Khuan Yew Chow oversaw the Singapore Cancer Registry and provided the data linkage for cancer outcomes. Thomas Wong and Wei-Yen Lim performed the data analyses and drafted the manuscript. All authors

**Table 4**  
Crude and multivariate adjusted HRs and 95% confidence intervals for obesity and risk of colorectal, colon and rectal cancer.

Exposure Variable	Colorectal Cancer			Colon Cancer		Rectal Cancer	
	Number of Cases	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>	Crude HR	Adjusted HR <sup>1</sup>
<b>Body Mass Index</b>							
Continuous		1.01 (0.99 – 1.02)	1.01 (1.00 – 1.01)	1.01 (1.00 – 1.02)	1.01 (1.00 – 1.02)	1.00 (0.96 – 1.03)	1.00 (0.97 – 1.03)
Underweight	27	1.10 (0.74 – 1.65)	1.06 (0.70 – 1.59)	1.16 (0.70 – 1.94)	1.09 (0.65 – 1.83)	1.02 (0.52 – 1.97)	1.01 (0.52 – 1.96)
Normal	172	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Overweight	260	1.11 (0.92 – 1.35)	1.11 (0.92 – 1.35)	1.25 (0.98 – 1.59)	1.26 (0.98 – 1.60)	0.90 (0.66 – 1.24)	0.90 (0.65 – 1.23)
Obese	157	1.31 (1.05 – 1.63)	1.39 (1.12 – 1.74)	1.52 (1.16 – 1.99)	1.64 (1.24 – 2.16)	0.99 (0.69 – 1.44)	1.03 (0.70 – 1.51)
	<i>P</i> <sub>trend</sub>	0.02	0.010	< 0.01	< 0.01	0.79	0.88
<b>Waist Circumference (cm)<sup>2</sup></b>							
Continuous		1.02 (1.01 – 1.02)	1.02 (1.01 – 1.03)	1.02 (1.01 – 1.03)	1.03 (1.01 – 1.05)	1.00 (0.99 – 1.01)	1.00 (0.98 – 1.02)
< 74.1	123	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
74.1 – 80.1	141	1.15 (0.90 – 1.46)	1.14 (0.88 – 1.47)	1.44 (1.05 – 1.98)	1.44 (1.03 – 2.00)	0.81 (0.55 – 1.19)	0.80 (0.53 – 1.21)
80.2 – 87.1	168	1.40 (1.11 – 1.77)	1.38 (1.05 – 1.81)	1.78 (1.31 – 2.40)	1.76 (1.24 – 2.49)	0.97 (0.67 – 1.41)	0.94 (0.61 – 1.47)
> 87.2	184	1.60 (1.27 – 2.01)	1.62 (1.17 – 2.25)	2.09 (1.56 – 2.82)	2.14 (1.42 – 3.25)	1.03 (0.71 – 1.49)	1.02 (0.59 – 1.76)
	<i>P</i> <sub>trend</sub>	< 0.01	< 0.01	< 0.01	< 0.01	0.70	0.81
<b>Waist–Hip Ratio<sup>2</sup></b>							
Recommended Cut-Off							
< 0.85	396	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
> 0.85	220	1.43 (1.21 – 1.69)	1.33 (1.12 – 1.57)	1.62 (1.32 – 1.98)	1.50 (1.22 – 1.84)	1.10 (0.82 – 1.48)	1.05 (0.77 – 1.42)
Quartile							
< 0.77	122	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.77 – 0.80	137	1.14 (0.89 – 1.45)	1.08 (0.84 – 1.38)	1.21 (0.89 – 1.66)	1.14 (0.83 – 1.56)	1.03 (0.70 – 1.52)	1.00 (0.67 – 1.47)
0.81 – 0.86	174	1.52 (1.20 – 1.91)	1.39 (1.10 – 1.75)	1.70 (1.27 – 2.29)	1.54 (1.15 – 2.08)	1.25 (0.86 – 1.82)	1.18 (0.80 – 1.74)
> 0.87	183	1.62 (1.28 – 2.03)	1.44 (1.14 – 1.83)	1.97 (1.48 – 2.62)	1.74 (1.30 – 2.34)	1.11 (0.75 – 1.64)	1.03 (0.68 – 1.56)
	<i>P</i> <sub>trend</sub>	< 0.01	< 0.01	< 0.01	< 0.01	0.41	0.70
<b>Waist–Height Ratio<sup>2</sup></b>							
Recommended Cut-Off							
< 0.5	178	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
> 0.5	438	1.39 (1.17 – 1.66)	1.30 (1.07 – 1.57)	1.77 (1.41 – 2.22)	1.66 (1.30 – 2.12)	0.93 (0.70 – 1.23)	0.85 (0.63 – 1.15)
Quartile							
< 0.48	123	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
0.48 – 0.51	139	1.17 (0.92 – 1.49)	1.15 (0.89 – 1.48)	1.34 (0.98 – 1.83)	1.31 (0.95 – 1.80)	0.94 (0.63 – 1.38)	0.96 (0.63 – 1.47)
0.52 – 0.57	172	1.44 (1.14 – 1.81)	1.38 (1.05 – 1.80)	1.77 (1.32 – 2.37)	1.65 (1.20 – 2.26)	1.01 (0.69 – 1.48)	1.05 (0.66 – 1.67)
> 0.88	182	1.58 (1.26 – 1.99)	1.57 (1.13 – 2.17)	1.88 (1.40 – 2.52)	1.80 (1.26 – 2.57)	1.18 (0.82 – 1.71)	1.33 (0.75 – 2.38)
	<i>P</i> <sub>trend</sub>	< 0.01	< 0.01	< 0.01	< 0.01	0.34	0.34

<sup>1</sup> Adjusted for age at baseline (continuous), housing type (HDB [1–3 rooms], HDB [≥ 4 rooms], private housing), race (Chinese, Malay, Indian, Others).

<sup>2</sup> Additionally adjusted for Body Mass Index.

reviewed the manuscript, provided comments and approved this submission.

## Declaration of interests

Dr Min-Han Tan is currently the CEO of Lucence Diagnostics Pte Ltd. His involvement in this study predated this appointment, and the content of this study is not related, directly or indirectly, to any products being offered by Lucence Diagnostics. The other authors have no interests to declare.

## References

- [1] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, *CA J. Clin. Oncol.* 61 (2011) 69–90.
- [2] J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, et al., Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11, International Agency for Research on Cancer, Lyon, France, 2013.
- [3] M.A. Hayat, Colorectal cancer, in: M.A. Hayat (Ed.), *Methods of Cancer Diagnosis, Therapy and Prognosis*, Springer, Netherlands, 2009, pp. 3–9.
- [4] M. Campbell-Thompson, I.J. Lynch, B. Bhardwaj, Expression of estrogen receptor (ER) subtypes and ERbeta isoforms in colon cancer, *Cancer Res.* 61 (2001) 632–640.
- [5] J. Hartman, K. Edvardsson, K. Lindberg, et al., Tumor repressive functions of estrogen receptor beta in SW480 colon cancer cells, *Cancer Res.* 69 (2009) 6100–6106.
- [6] A. Barzi, A.M. Lenz, M.J. Labonte, H.-J. Lenz, Molecular pathways: estrogen pathway in colorectal cancer, *Clin. Cancer Res.* 19 (21) (2013), <https://doi.org/10.1158/1078-0432.CCR-13-0325>.
- [7] R.T. Chlebowski, J. Wactawski-Wende, C. Ritenbaugh, F.A. Hubbell, J. Ascensao, R.J. Rodabough, Estrogen plus progestin and colorectal cancer in postmenopausal women, *N. Engl. J. Med.* 350 (March (10)) (2004) 991–1004.
- [8] M.M. Symer, N.Z. Wong, J.S. Abelson, J.W. Milsom, H.L. Yeo, Hormone replacement therapy and colorectal Cancer incidence and mortality in the prostate, lung, colorectal, and ovarian cancer screening trial, *Clin. Colorectal Cancer* 17 (June (2)) (2018) e281–e288, <https://doi.org/10.1016/j.clcc.2018.01.003>.
- [9] K.K. Tsilidis, N.E. Allen, T.J. Key, et al., Oral contraceptives, reproductive history and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition, *Br. J. Cancer* 103 (2010) 1755–1759.
- [10] G.C.M.A. Kabat, T.E. Rohan, Oral contraceptive use, hormone replacement therapy, reproductive history and risk of colorectal cancer in women, *Int. J. Cancer* 122 (2008) 643–646.
- [11] A.C. Lo, A.S. Soliman, H.M. Khaled, A. Aboulyazid, J.K. Greenon, Lifestyle, occupational, and reproductive factors and risk of colorectal cancer, *Dis. Colon Rectum* 53 (2010) 830–837.
- [12] N. Murphy, L. Xu, A. Zervoudakis, X. Xue, G. Kabat, T.E. Rohan, S. Wassertheil-Smoller, et al., Reproductive and menstrual factors and colorectal cancer incidence in the Women's Health Initiative Observational Study, *Br. J. Cancer* 116 (January (1)) (2017) 117–125, <https://doi.org/10.1038/bjc.2016.345> Epub 2016 Nov 29.
- [13] A. Zervoudakis, H.D. Strickler, Y. Park, et al., Reproductive history and risk of colorectal Cancer in postmenopausal women, *JNCI J. Natl. Cancer Inst.* 103 (10) (2011) 826–834, <https://doi.org/10.1093/jnci/djr101>.
- [14] K. Tamakoshi, K. Wakai, M. Kojima, et al., A prospective study of reproductive and menstrual factors and colon cancer risk in Japanese women: findings from the JACC study, *Cancer Sci.* 95 (2004) 602–607.
- [15] Y. Lu, J. Oddsberg, A. Martling, J. Lagergren, Reproductive history and risk of colorectal adenocarcinoma, *Epidemiology* 25 (2014) 595–604.
- [16] M. Kyrgiou, I. Kalliala, G. Markozannes, et al., Adiposity and cancer at major anatomical sites: umbrella review of the literature, *BMJ* 356 (2017), <https://doi.org/10.1136/bmj.j477>.
- [17] A.G. Renehan, M. Zwahlen, M. Egger, Adiposity and cancer risk: new mechanistic insights from epidemiology, *Nat. Rev. Cancer* (15) (2015) 484–498.
- [18] Y. Dong, J. Zhou, Y. Zhu, T. He, H. Hu, H. Liu, et al., Abdominal obesity and colorectal cancer risk: systematic review and meta-analysis of prospective studies, *Biosci. Rep.* 37 (December (6)) (2017), <https://doi.org/10.1042/BSR20170945> Published 2017 Dec 12.
- [19] M. Keimling, A.G. Renehan, G. Behrens, B. Fischer, A.R. Hollenbeck, A.J. Cross, M.F. Leitzmann, Comparison of associations of body mass index, abdominal adiposity, and risk of colorectal cancer in a large prospective cohort study, *Cancer Epidemiol. Biomarkers Prev.* 22 (2013) 1383–1394.
- [20] WHO Expert Consultation Group. Appropriate body-mass index for Asian

- populations and its implications for policy and intervention strategies, *Lancet* 363 (2004) 157–163.
- [21] E.H. Ng, F.C. Ng, P.H. Tan, et al., Results of intermediate measures from a population-based, randomized trial of mammographic screening prevalence and detection of breast carcinoma among Asian women: the Singapore Breast Screening Project, *Cancer* 82 (1998) 1521–1528.
- [22] National Registry of Diseases Office Singapore, Singapore Cancer Registry Report No 8. Cancer incidence and Mortality 2003-2012 and Selected Trends 1973-2012 in Singapore, (2015).
- [23] World Health Organization, Waist Circumference and Waist-hip Ratio : Report of a WHO Expert Consultation, Geneva, 8-11 December 2008, World Health Organization, Geneva, 2011.
- [24] S.D. Hsieh, H. Yoshinaga, T. Muto, Waist-to-height ratio, a simple and practical index for assessing central fat distribution and metabolic risk in Japanese men and women, *Int. J. Obes. Relat. Metab. Disord.* 27 (May (5)) (2003) 610–616.
- [25] Y.S. Khader, A. Batiha, H. Jaddou, Z. Batiha, M. El-Khateeb, K. Ajlouni, Anthropometric cutoff values for detecting metabolic abnormalities in Jordanian adults, *Diabetes Metab. Syndr. Obes.* 3 (2010) 395–402.
- [26] StataCorp, Stata Statistical Software: Release 11, StataCorp LP, College Station, TX, 2009.
- [27] T.V. Clendenen, K.L. Koenig, R.E. Shore, M. Levitz, A.A. Arslan, A. Zeleniuch-Jacquotte, Postmenopausal levels of endogenous sex hormones and risk of colorectal Cancer, *Cancer Epidemiol. Biomarkers Prev.* 18 (1) (2009) 275–281, <https://doi.org/10.1158/1055-9965.EPI-08-0777>.
- [28] C.Y. Li, B. Song, Y.Y. Wang, et al., Age at menarche and risk of colorectal cancer: a meta-analysis, *PLoS One* 8 (2013) e65645.
- [29] J. Lin, S.M. Zhang, N.R. Cook, J.E. Manson, J.E. Buring, Lee I. Oral Contraceptives, Reproductive factors, and risk of colorectal cancer among women in a prospective cohort study, *Am. J. Epidemiol.* 165 (2007) 794–801.
- [30] S. Neumeyer, B.L. Banbury, V. Arndt, S.I. Berndt, S. Bezieau, Bien SA Mendelian randomisation study of age at menarche and age at menopause and the risk of colorectal cancer, *Br. J. Cancer* 118 (June (12)) (2018) 1639–1647, <https://doi.org/10.1038/s41416-018-0108-8> Epub 2018 May 24.
- [31] S.C. Larsson, A. Wolk, Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies, *Am. J. Clin. Nutr.* 86 (2007) 556–565.
- [32] Z. Dai, Y.C. Xu, L. Niu, Obesity and colorectal cancer risk: a meta-analysis of cohort studies, *World J. Gastroenterol.* 13 (2007) 4199–4206.
- [33] A.A. Moghaddam, M. Woodward, R. Huxley, Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events, *Cancer Epidemiol. Biomarkers Prev.* 16 (2007) 2533–2547.
- [34] T. Pischon, P.H. Lahmann, H. Boeing, et al., Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC), *JNCI* 98 (2006) 920–931.
- [35] H. Li, G. Yang, Y.B. Xiang, et al., Body weight, fat distribution and colorectal cancer risk: a report from cohort studies of 134 255 Chinese men and women, *Int. J. Obes. (Lond.)* 37 (2012) 783–789.
- [36] H. Freisling, M. Arnold, I. Soerjomataram, M.G. O'Doherty, J.M. Ordóñez-Mena, C. Bamia, et al., Comparison of general obesity and measures of body fat distribution in older adults in relation to cancer risk: meta-analysis of individual participant data of seven prospective cohorts in Europe, *Br. J. Cancer* 116 (May (11)) (2017) 1486–1497, <https://doi.org/10.1038/bjc.2017.106> Epub 2017 Apr 25.
- [37] L.L. Moore, M.L. Bradlee, M.R. Singer, G.L. Splansky, M.H. Proctor, R.C. Ellison, B.E. Kreger, BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults, *Int. J. Obes. Relat. Metab. Disord.* 28 (4) (2004) 559–567.