Anthropometrics, body shape over 12 years and risk of cancer events in pre- and post-menopausal women.

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Abbreviations:

BMI- Body mass index

WC- Waist circumference

HC- Hip circumference

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Key words

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Brief description of findings:

In this large population of women of lean stature, with numerous anthropometric characteristics measured over 12 years, height and waist circumference were related to cancer risk, while BMI, after waist and hip circumferences were adjusted for, was not. Height was associated with an increase in cancer risk both before and after menopause, independent of other anthropometric characteristics. The relationship between cancer occurrence and waist circumference was different by menopausal status with a decreased risk before menopause, and an increased risk after. Height and waist circumference exert different and independent roles on cancer risk.

Abstract

Studies of anthropometry and cancer have focused on BMI. Relations between weight, waist and hip circumferences, birth length and adult height with cancer are less well studied. Women from the French E3N study, born between 1925-1950, were followed biennially from 1995 until 2008. Body shape was classed into four groups based on median waist (WC) and hip (HC) circumferences at baseline. Hazard ratios (HRs) were estimated by Cox proportional hazards regression models. Over the 12 years of follow-up, 7,247 of 63,798 women developed cancer.

As WC increased, we found a trend for decreasing cancer risk in pre-menopausal women, which reversed to an increasing risk in post-menopausal women. This remained unchanged after further adjustment for HC /or height [HR: 0.72 (0.52–1.00) before menopause and 1.17 (1.04–1.31) in the 5^{th} vs. 1^{st} quintile of HC], and were similar after exclusion of breast cancer. We showed that large body shape decreased cancer risk before menopause and increased it after [HR: 0.87 (0.73–1.02) and 1.11 (1.04–1.17) respectively, in women with large waist and hips compared to small waist and hips]. Adult height was associated with an non significant increase in cancer in pre-menopause and a significant cancer risk in menopause, independent of other anthropometric characteristics [5^{th} vs. 1^{st} quintile [HR: 1.24 (0.98 – 1.56) and 1.20 (1.10–1.30)], respectively as was long birth length in post menopausal women [HR: 1.18(1.07–1.30) compared to medium birth length]. These results suggest independent roles of height and WC on cancer risk, through different pathways.

259 words

Introduction

The relationship between adiposity and cancer has been well described using body mass index (BMI) as a surrogate for body fat distribution[1]. However, there are still some inconsistencies in the data in that not all studies report the same findings.[1, 2] Anthropometric markers of visceral obesity such as waist circumference (WC),[3, 4] and waist-to-hip ratio (WHR),[5, 6] have also been shown to be positively related with cancer, suggesting that most of the pathological influence of adiposity is due to visceral, rather than subcutaneous, fat. Other markers such as hip circumference (HC) and height have been less well-studied. HC has been shown to be inversely associated with blood glucose, blood pressure and lipids[7, 8] and is also associated with a reduced risk of all-cause[9, 10] and cardiovascular mortality,[11, 12] particularly when adjusted for WC.[10, 13, 14] Furthermore, a specific protective role of gluteofemoral body fat (adiposity around the hips), which is thought to primarily occur via the regulation of fatty acid release and uptake, and a beneficial adipokine profile, is also now being recognised.[15]

While WHR attempts to capture the risk associated with a differential fat distribution, its ability to examine non-linear relationships is limited.[16] Analysing WC and HC in the same model may thus provide a better assessment of body shape and we showed recently that the effect of central obesity on mortality risk is underestimated without adjustment for HC.[15,16] WC adjust ed for HC may thus be a better determinant of cancer risk than WC alone. However, data exploring this concept are sparse.

Recent studies have also shown an increased risk of adult cancer associated with greater birth length, but these studies have not controlled for adult central adiposity, as reviewed in Green *et al.*[17] Moreover, these studies have only examined markers at a single time point and have not considered a changing body shape over the lifetime.

We used data from a large prospective study to explore the relationships between various anthropometric characteristics that were regularly updated over a 12 year period of the adult lifecourse, and the development of cancer.

Material and Methods

The E3N cohort Study

The ‘Etude Epidémiologique auprès des Femmes de la Mutuelle Générale de l’Education Nationale’ (E3N) prospective cohort was initiated in 1990 when 98,995 women living in France, aged 40-65 years at recruitment, were recruited from the national teachers’ health insurance plan.[18] All women provided informed consent in

accordance with the rules of the French National Commission for Data Protection and Individual Freedom (Commission Nationale Informatique et Libertés) from which approval was obtained. Nine self-administered questionnaires were completed up to now, approximately every 24-36 months, and they provided data on lifestyle and reproductive factors, and on the occurrence of various health events including cancer. Dietary data was also collected between June 1993 and July 1995 (Q3) for 74,531 women, by a validated diet history questionnaire, from which patterns of “healthy” and “western” diet were derived[18]. Menopausal status was classified by information collected by self-report. In brief, women were considered postmenopausal if they had had 12 consecutive months without a menstruation (unless due to hysterectomy), had undergone bilateral oophorectomy, had used menopause hormone therapy (MHT) or had self-reported that they were postmenopausal. We defined the date of menopause as: the date preceding 12 consecutive months of amenorrhea (unless due to hysterectomy or if the last menstrual period occurred before MHT use); the date of bilateral oophorectomy or, if not available, in decreasing order of priority: self-reported date of menopause, date when MHT use began, date when menopausal symptoms began or, if no information was available, the date corresponding to age 47 if menopause was artificial, or age 51 otherwise.

Assessment of anthropometric measurements

Self-reported weight was obtained from each of the nine questionnaires, self-reported height from the 1st questionnaire, 4th questionnaire, 6th questionnaire and 7th questionnaire,and the average height was used. Self-reported WC and HC were collected in the 4th and 7th questionnaire. Women were asked to measure their WC using detailed instructions. WC was determined as the smallest circumference between the base of the ribs and the largest point of the iliac crest, while HC was the largest circumference below the umbilicus[18].

BMI was computed as weight/(height*height) in kg/m^2 from the weight recorded in each questionnaire..

Women were asked to self-report their birth length and weight into small, medium or large categories and if possible to provide an estimated birth weight and length. For those who did provide length and/or weight data, the cutpoints used were for length: short (<48 cm), medium (48–51 cm) and large (≥51 cm), and for weight: small (<2500

g), medium (2500–4000 g) and large (≥4000 g). Analyses using these variables were performed only among those who responded to the questionnaires. A total of 22.4% and 19.4% of the cancer and non cancer events, respectively, had missing data for birth length. For birth weight, 15.2% and 11.6% were missing these data, respectively.

Assessment of cancer cases

Participants were asked to report any diagnosis of cancer on each follow-up questionnaire, and we systematically requested pathology reports from the patients or their doctors. Pathology reports were obtained for over 90% of the identified incident cases. Deaths were identified from the family and/or insurance files. Causes of death were obtained from the French National Service on Causes of Death (http://www.cepidc.vesinet.inserm.fr/).

Study population

Follow-up started in 1995, the date of return of the 4th questionnaire. Responders (n=69,149) contributed person-years of follow-up until their date of death or the date of any cancer diagnosis, the date of the last completed questionnaire or June 2008, which ever occurred first. Finally, data were available for 63,798 women for these analyses, and 51,619 women provided birth length and weight data.

Statistical analysis

All analyses used the Statistical Analyses Systems (SAS) version 9.2 (SAS Institute, Inc., Cary, NC). All reported statistical tests are two sided. Descriptive statistics: medians and percentages were compared using Mood's median and Pearson's χ^2 squared tests as appropriate. All analyses have been stratified according to menopausal status, as previous studies including the E3N cohort have shown interactions between BMI and menopausal status for breast cancer.[19]We tested interactions between all other exposures including body shape with menopausal status on the development of cancer. Given the lack of statistical power inherent in interaction tests, we used a p-value cut point of p=0.2.[20, 21] Cox proportional hazards regression analysis, with age as the time scale, was used and we report hazard ratios (HR) and

95% confidence intervals. To test for linear trends across quintiles, we assigned ordinal values to each quintile group, and we report p_{trend} values.

Anthropometric characteristics (weight, BMI, WC, HC), lifestyle factors (smoking status), menopausal status, diabetes, and history of coronary heart disease (CHD) were considered as time-dependent variables. The exposures were modelled according to quintiles of the anthropometric markers defined at baseline, unless otherwise indicated. adjusted our models for potential confounding factors: alcohol intake (g/day), total physical activity (Met-h/week), smoking status (never, ex and current smokers), educational level, prior history of CHD, diabetes status, dietary pattern, oral contraceptive use, menopause hormone therapy (MHT, among post-menopausal women). Models for one particular anthropometric characteristic were also adjusted for an additional one, as indicated in footnotes of the tables. There were no significant interactions between WC and HC, BMI and HC or WC and height.

Women were also grouped into four categories of body shape which combined low versus high HC with low versus high WC based on the median value of WC (79 cm) and HC (98 cm) at baseline.

Sensitivity analyses

A sensitivity analysis excluded all cases of cancer diagnosed within 2 years after the start of follow-up. Further sensitivity analyses excluded infants born prematurely.

Results

We analysed 63,798 women corresponding to 746,947 person years, with a median follow-up of 12 years during which 7,247 incident cancers occurred. Analyses on birth weight and length were restricted to the subset of women (n= 51,614) who provided birth data.

Women who developed cancer were older than those who did not 54.9 years (10.7) vs. 53.1 (10.5) at baseline) and were more frequently smokers (12% vs. 11% current smokers at baseline). Educational level was similar among the two groups. Table 1 describes the characteristics at baseline according to those who did and did not have a cancer diagnosed over follow-up. While anthropometric parameters differed in terms of statistical significance, they were similar in magnitude in the two groups. Birth length and weight differed in those who had a cancer event versus those who did not.

We observed significant interactions between weight (p=0.060), BMI (p=0.003), birth weight (p=0.009), birth length (0.027), and body shape (0.055) and menopausal status. The interaction test with WC (p=0.136) was not significant but met our *a priori* criteria for stratification. Interactions with height (p=0.657) and HC (0.373) were not significant but to avoid hypotheses generating, we stratified all exposure variables by menopausal status.

Among the 7247 cancers events which occurred during follow-up, breast cancer was the most common cancer accounting for 48% of all cancer followed by skin (11.4%), digestive organs cancers (7.6%), uterus (5.3%), ovary (3.0%), thyroid (3.4%), lungs (2.7%), unknown type (3.5%) and others (15.2%).

Adult height

Adult height was related to an increased risk of cancer. In pre-menopausal women, the risk was of borderline significance and was only significantly increased after adjustment for WC [HR: 1.24 (0.98 – 1.56), 5^{th} vs. 1^{st} quintile]. In post-menopausal women, compared to those with height below the 1^{st} quintile, women with height above the 5^{th} quintile were at a higher risk of cancer [HR: 1.22 (1.12 – 1.32)]. When height was modelled in a continuous form, the risk of cancer increased with increasing height (p_{trend} <0.0001; 1.12 (1.09 – 1.17) for a 10 cm increment in height). These relationships changed little after adjustment for WC [HR: 1.20 (1.10 – 1.30)], HC [HR: 1.19 (1.10 – 1.30)] (Table 2) or weight [HR: 1.14 (1.05 – 1.25)].

Adult weight

In pre-menopausal women, there was no significant relationship between weight and cancer, while in post-menopausal women the risks increased significantly in the 3^{rd}, 4^{th} and 5^{th} quintiles and increased with increasing weight. The HR of the 4th quintile lost significance with adjustment for WC (Table 2). Adjustment for HC did not change the results for weight materially.

Body Mass Index

A higher BMI was associated with a lower risk of cancer in pre-menopausal women. Compared to women with BMI below the 1^{st} quintile, pre-menopausal women with BMI in the 4^{th} and 5^{th} quintile groups had lower risks of cancer: HR: 0.79 (0.63 –

0.98) and HR: 0.65 (0.51 – 0.81), respectively, and this association changed little after adjustment for HC or WC.

After menopause, an increase in risk was seen with increasing BMI (p_{trend} across quintiles <0.0004), with a HR of developing cancer for post-menopausal women in the 5th quintile compared to those of the 1st quintile, 1.14 (1.06 – 1.23); this association was attenuated and lost significance after adjusting for HC or for WC (Table 2).

Waist and hip circumferences

Pre-menopausal women with WC above the top quintile had a lower risk of cancer [HR: 0.77 (0.60 – 0.98)], p_{trend} = 0.006, a result that was slightly attenuated on adjusting for HC [HR: 0.72 (0.52 – 1.00)], p_{trend} = 0.01. Conversely, after menopause, cancer risk increased with WC (p_{trend} <0.0001 and HR in the 5th quintile compared to the 1st, 1.24 (1.14 – 1.35)). The magnitude of the HR in the 5th WC quintile was attenuated slightly after adjustment for HC but remained significant (Table 3). The addition of BMI or adult height had little effect in post-menopausal women, but in pre-menopausal women, the relation lost significance.

There was no significant relationship between HC and risk of cancer in pre-menopausal women. Post-menopausal women with HC in the 4th [HR: 1.09 (1.00 – 1.18)] or 5th [HR: 1.17(1.7 – 1.27)] quintile were at increased risk independent of adult height, but HRs lost significance upon the addition of WC or BMI.

Body shape

Compared to women who have small hips and waist (thin stature), those having large hips and large waist were at decreased cancer risk in the pre-menopause period, of borderline significance [HR: 0.87 (0.73 – 1.02)], and this was slightly attenuated after addition of adult height or BMI. Those with a small waist and large hips were at increased risk, but only after addition of BMI. Post-menopausal women with large hips and large waist body shape were at significantly increased risk [HR: 1.11 (1.04 – 1.17)] independent of adult height, but the result was attenuated further with adjustment for BMI. Other groups did not differ from the reference category (Table 3).

Birth weight and length

We found no association between birth weight with pre- or post-menopausal cancer incidence. All results were not materially different when premature babies were excluded from the analyses (Table 4).

In pre-menopausal women, birth length was not significantly associated with cancer development. After menopause, compared to medium birth length, small birth length was associated with a decreased risk of cancer [HR: 0.90 (0.82 – 0.98), but this result lost significance and became attenuated upon adjustment for adult height [HR: 0.96 (0.88 –1.05)]. Long birth length was associated with an increase risk [HR in adjusted models: 1.18 (1.07 – 1.30)]. Adjustment for adult height only slightly attenuated this association [HR: 1.11 (1.00 – 1.23)], but with the addition of BMI [HR: 1.10 (0.99 – 1.22)] or WC [HR: 1.08(0.97 – 1.20)], the results became borderline significant. When the model with birth weight is adjusted for birth length and vice versa, the results are similar.

Further, the results did not differ by adult smoking status, nor by education status (data not shown). We were unable to show any association between birth weight and cancer incidence. All results did not differ when premature babies were excluded from the analyses.

In sensitivity analyses where deaths or cancer diagnosis occurring in the first two years were excluded, the results for all modelled exposures were not materially different. Finally, sensitivity analyses were conducted whereby the models with WC and BMI (in quintiles) were repeated with the exclusion of breast cancer cases. Again the results did not differ (data not shown). Lastly, a sensitivity analysis was performed where exposures of BMI were not updated over time and the results did not differ (data not shown).

Discussion

In this large cohort of French, middle-aged women, we showed that as WC or BMI / weight increased, there was a trend for decreasing cancer risk in pre-menopausal women, which reversed to an increasing risk in post-menopausal women. Consistent with these findings, we showed that large body shape (large waist and hips) decreased cancer risk before menopause and increased it after. Lastly, we showed that height, at birth and when adult, was a risk factor for cancer, both before and after menopause, independent of other anthropometric characteristics.

While the evidence linking elevated WC to adverse outcomes is increasing, less is known about the combined effect of both WC and HC. We found little difference in the magnitude of the HR with and without HC, thus failing to confirm our hypothesis, which could not support the findings of others that the addition of HC provides a better discrimination of risk of cancer than WC alone.[10, 13, 14] Interestingly, HC alone was associated with an increased risk of cancer which was attenuated and lost significance upon the addition of WC into the model. Several studies have reported an inverse association of HC with risk of diabetes,[2] CVD, and all-cause mortality.[16] Although the cancer data on HC is sparse, in this same cohort, we have previously reported that HC alone increases breast cancer risk,[7] which appears contradictory to other data. In other cohorts, we recently showed that WC, adjusted for HC, improved risk prediction compared to WC alone for CVD mortality in 9000 individuals from Mauritius. [2,16,19,] To our knowledge, our analysis is the first report on the combined impact of WC and HC for cancer and it may be that the protective role of large hips is only relevant for diabetes,[2] CVD and all-cause mortality outcomes.[16]

We also examined whether body shape, as defined by various combinations of WC and HC was a risk factor of cancer. Excess cancer risk conferred by large body shape (large waist and hips) is consistent with the notion that the protective role of large hips may be confined to non-cancer outcomes. For pre-menopausal women, large hips and large waist were associated with a borderline decrease in risk. Similar results have been observed for breast cancer risk.[19] The proposed biological reason underlying a decreased cancer risk is that in pre-menopausal overweight and obese women, levels of the active estrogen hormone, estradiol, may be relatively low due to a decreased hormone production capacity or rapid clearance of hormones by the liver, or other tissues, through unknown mechanisms[22] Recent data, however, suggest that the latter

relationship may be confounded by mammary density, which is inversely related to body size and is related to breast cancer risk.[22]

Few studies have reported on anthropometric features or body shape over a long period (> 12 years). Large body shapes (large hips and large waist) in adult life have been associated with colon adenoma[23] which is consistent with our findings. However Morois *et al.*[23] analysed body shape at various different times of the life-course using body silhouettes rather than body measurements.

Our results of WC adjusted for HC are very similar to the body shape results. From a clinical perspective however, the body shape variable provides a message that may be easier to interpret and apply clinically than trying to understand a person's cancer risk of large WC adjusted for their HC.

We also observe that height (both birth length and adult height) are associated with increased risk of cancer in post-menopausal women. This finding was independent of confounding factors and was unaffected upon the exclusion of prematurely born infants from the analyses. The association of adult height on incident cancer has been shown in several studies.[24-26] Recently, the 'Million Women Study' showed that tall women were at increased risk of cancer after adjustment for confounding factors, with HR of any cancer of 1.16 (1.14 – 1.17) per 10 cm increase in height, a result similar to ours in magnitude (HR: 1.12 (1.07 – 1.19) per 10 cm). They also found that the association was stronger in non-smokers. Our results differ from this study and the accompanying meta-analysis in several ways. Firstly, we observed this relationship only in post-menopausal women, secondly we did not observe a difference in smokers and non-smokers and thirdly, although Renehan[27] report that socio-economic status may confound or effect modify the relationship between height and cancer, we and other authors[17] did not observe a similar effect. We were also able to show that adult height was related to cancer risk, independently of WC. Furthermore, we show that longer birth length increased cancer risk independently of adult height in post-menopausal women. In addition, babies with smaller birth lengths were protected from cancer in post-menopausal women only. Birth length has been shown to be a predictor of breast cancer risk in three other studies, all with much smaller samples[28], as well as in a meta-analysis.[29] The biological mechanisms underlying the relationship between birth size and cancer risk are not known. However, for breast cancer, it has been proposed that birth size correlates with foetal estrogen exposure and with maternal levels of other

growth factor hormones. These hormones may alter programming of the breast tissue, making it more susceptible to cancer initiation by other hormones later in life[29].

We were unable to show any relationship between birth weight, and cancer. Birth weight has been associated with several cancers including breast cancer [29] and leukaemia.[30] It is unlikely that the lack of significant findings of birth weight and cancer is due to difficulties in accuracy introduced by self-report, lack of sufficient range and/or variability of birth weight measurements since Morois et al., 2011[23] have observed that birth weight is related to risk of colon adenoma in the E3N cohort. It is possible however that the differences could be due to unmeasured confounding and perhaps a different set of covariates variable used in each study.

There are several mechanisms whereby height may be associated with the development of cancer. Growth hormones such as insulin-like growth factors (IGFs) have been implicated. These hormones, in both childhood and adulthood, have been associated with increased cancer risk[17] and circulating levels in children and adolescents have been associated with increased skeletal growth.[31] Levels of IGFs have also been associated with adult height. It has been suggested that high circulating levels of such growth factors could lead to increased cell turnover and a larger number of cells,[17] and as tall individuals have a larger number of cells, in particular stem cells, this may lead to a greater propensity to develop malignancies.[32, 33] Prospective studies with measures of growth hormones and cancer outcomes are required to further explore mechanisms involved in the current limited evidence reporting associations between height and the development of cancer.

Strengths and limitations

The strengths of our study include a prospective design, good response rates, a large population and the biennial updating of risk factor status throughout 12 years of follow-up. The self-reporting of anthropometric measures is a potential limitation of this study, however, in a validation study of self-measured and self-reported anthropometric data compared to data measured by trained staff, the correlation coefficients of all anthropometric measures were greater than 0.8 with a maximum of 0.94 for height.[34] Further, we believe any misreporting of data would lead to non-differential errors which would serve to dilute any effects towards the null. Other limitations relate to the homogeneity of the sample. Given that the women from this study were recruited using a teacher's registry, these women may represent a homogenous group in terms of

social class and thus our ability to observe effects by socioeconomic status may be limited. We also note that there was missing data on birth weight and length, especially in women who had died; however since birth length was not related to mortality (data not shown), it unlikely that this affected our results.

Conclusion

In our large population of women of lean stature, with numerous anthropometric characteristics measured over 12 years, we found that height and waist circumference, were related to cancer risk and was unaffected by the addition of HC. The relationship with WC was different by menopausal status, with, a trend for decreasing cancer risk in pre-menopausal women, which reversed to an increasing risk in postmenopausal women. These results suggest that the risk of cancer may be different as women age. Further studies, on populations of similar stature, are required to confirm or refute our findings.

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Table 1. Characteristics of the study population at baseline according to cancer in the E3N cohort, 1995-2008.

	All cancers		
	Fatal or non-fatal cancer (n=7,247)	**No cancer event (n=56,551)**	***p* values [1]**
Height (cm)	162.0 (8.0)	162.0 (7.0)	0.0005
Weight (kg)	60.0 (11.0)	59.0 (11.0)	0.0003
Waist circumference (cm)	75.0 (12.0)	75.0 (10.0)	0.0014
Hip circumference (cm)	96.0 (10.0)	96.0 (10.0)	0.0004
BMI (kg/m²)	22.7 (4.0)	22.6 (3.9)	0.0007
Birth length [2]			<0.0001
Small	8.2	9.7	
Medium	62.4	64.8	
Large	6.9	6.1	
Birth weight (%)[2]			<0.0001
Small	11.2	12.4	
Medium	62.2	64.7	
Large	11.4	11.2	
Age (years)	53.1 (10.5)	<0.0001	54.9 (10.7)
Education (secondary or higher)	35.2	34.4	0.3058
Smoking	12.1	11.1	0.0459
Prior history of CHD	0.6	0.7	0.349
Post-menopause	69.2	62.7	<0.0001
Diabetes	1.2	1.3	0.6460
Physical activity (Mets–h/week)	49.2 (39.5)	48.5 (39.0)	0.1179
Alcohol intake (g/day)	6.3 (14.5)	6.1 (14.3)	0.1309

Data are median (IQR) or %. [1]*p* values for Mood's test for comparison of medians for continuous variables, and Chi² test for categorical variables. [2]Analyses were only conducted in those who responded to the questionnaires.

Table 2. Hazard ratios (95% CI) for all cancers according to height, weight and body mass index in pre- and post- menopausal women in the E3N cohort, 1995-2008.

	Hazard Ratio (95% CI)							
	Pre-menopausal women				Post-menopausal women			
Height (cm)	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Cases**	**Model 1**	**Model 2**	**Model 3**
<157	125	1	1	1	1121	1	1	1
157–160	100	1.00 (0.77 – 1.30)	1.07 (0.82-1.41)	1.08 (0.83 – 1.42)	927	1.06 (0.98 – 1.16)	1.08 (0.99-1.19)	1.08 (0.99 – 1.18)
160–163	192	1.14 (0.91 – 1.42)	1.16 (0.91-1.46)	1.18 (0.93 – 1.49)	1489	1.10 (1.02 – 1.19)	1.10 (1.01-1.19)	1.10 (1.02 – 1.20)
163–167	204	1.10 (0.88 – 1.38)	1.14 (0.90-1.44)	1.17 (0.92 – 1.47)	1504	1.14 (1.05 – 1.23)	1.13 (1.04-1.23)	1.14 (1.05 – 1.23)
≥167	221	1.15 (0.92 –1.43)	1.24 (0.99-1.57)	1.24 (0.98 – 1.56)	1364	1.22 (1.12 – 1.32)	1.19 (1.10-1.30)	1.20 (1.10 – 1.30)
p_{trend}		*0.1661*	*0.0632*	*0.0646*		*<0.0001*	*<0.0001*	*<0.0001*
Weight (kg)	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Cases**	**Model 1**	**Model 2**	**Model 3**
<54	161	1	1	1	1088	1	1	1
54–58	176	0.99 (0.80 –1.23)	0.97 (0.77–1.21)	1.02 (0.81–1.28)	1068	1.04 (0.95 – 1.13)	1.02 (0.93 – 1.12)	1.02 (0.93 – 1.11)
58–63	200	1.08 (0.87–1.33)	1.06 (0.84–1.33)	1.15 (0.91–1.44)	1413	1.12 (1.03 –1.21)	1.11 (1.02 – 1.21)	1.09 (1.00 – 1.19)
63–70	141	0.87 (0.70 –1.10)	0.87 (0.66 –1.14)	0.97 (0.75 –1.25)	1305	1.13 (1.04 –1.22)	1.10 (1.00 – 1.21)	1.07 (0.97 –1.17)
≥70	164	0.81 (0.65 –1.01)	0.83 (0.60 –1.15)	1.04 (0.77 –1.41)	1531	1.24 (1.14 –1.34)	1.19 (1.06 – 1.34)	1.14 (1.02 –1.27)
p_{trend}		*0.0522*	*0.2498*	*0.9067*		*<0.0001*	*0.0036*	*0.0216*
BMI (kg/m²)	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Cases**	**Model 1**	**Model 2**	**Model 3**
<20.7	218	1.00 (0.82 – 1.21)	1.05 (0.85 –1.30)	0.96 (0.77-1.19)	1148	1.00 (0.93 –1.09)	1.03 (0.95 –1.13)	1.05 (0.96-1.14)
20.7–22.4	173	0.84 (0.68 – 1.03)	0.84 (0.68 –1.04)	0.81 (0.65-1.01)	1236	1.00 (0.92 –1.08)	0.99 (0.92 –1.08)	1.01 (0.93-1.10)
22.4–23.9	193	1	1	1	1236	1	1	1
23.9–26.3	131	0.79 (0.63 – 0.98)	0.76 (0.60 – 0.95)	0.78 (0.62-0.99)	1364	1.07 (0.99 – 1.15)	1.03 (0.95 –1.12)	1.02 (0.94-1.11)
≥26.3	127	0.65 (0.51 – 0.81)	0.58 (0.44 – 0.76)	0.65 (0.50-0.85)	1421	1.14 (1.06 – 1.23)	1.04 (0.95 –1.14)	1.02 (0.93-1.12)
p_{trend}		*0.0005*	*0.0012*	*0.0519*		*0.0004*	*0.7362*	*0.7044*

Model 1: Adjusted for smoking, education, diabetes, alcohol intake, previous history of coronary heart disease, physical activity, dietary intake, use of oral contraceptives and use of hormone replacement therapy (only for post-menopausal women).
Model 2: Model 1 further adjusted on hip circumference.
Model 3: Model 1 further adjusted on waist circumference.

Table 3. Hazard ratios (95% CI) for all cancers according to waist circumference, hip circumference and body shape in pre- and post- menopausal women in the E3N cohort, 1995-2008.

Cancer	**Hazard Ratio (95% CI)**									
	Pre-menopausal women					**Post-menopausal women**				
Waist circumference (cm)	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
<71	174	1	1	1	1	935	1	1	1	1
71-76	204	1.06 (0.86-1.30)	1.04 (0.84-1.28)	1.04 (0.85-1.28)	1.12 (0.91-1.37)	1184	1.06 (0.97-1.15)	1.04 (0.96-1.14)	1.05 (0.96-1.14)	1.06 (0.97-1.15)
76-81	179	1.07 (0.86-1.32)	1.04 (0.83-1.31)	1.05 (0.85-1.29)	1.16 (0.93-1.45)	1162	1.14 (1.04-1.24)	1.11 (1.02-1.22)	1.12 (1.02-1.22)	1.13 (1.03-1.23)
81-88	131	0.88 (0.70-1.11)	0.84 (0.65-1.10)	0.87 (0.69-1.09)	1.03 (0.78-1.30)	1254	1.07 (0.98-1.16)	1.03 (0.94-1.14)	1.05 (0.96-1.14)	1.06 (0.96-1.16)
≥88	114	0.77 (0.60-0.98)	0.72 (0.52-1.00)	0.75 (0.59-0.96)	0.98 (0.71-1.35)	1524	1.24 (1.14-1.35)	1.17 (1.04-1.31)	1.20 (1.11-1.31)	1.21 (1.09-1.35)
P trend		*0.0064*	*0.0101*	*0.0032*	*0.669*		*<0.0001*	*0.0080*	*<0.0001*	*<0.0001*
Hip circumference (cm)	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
<91	162	1	1	1	1	947	1	1	1	1
91-95	187	1.14 (0.92-1.40)	1.17 (0.95-1.46)	1.12 (0.91-1.39)	1.21 (0.98-1.50)	931	1.02 (0.93-1.12)	1.00 (0.91-1.09)	1.01 (0.92-1.10)	1.01 (0.92-1.11)
95-100	160	1.00 (0.80-1.24)	1.09 (0.86-1.37)	0.97 (0.78-1.22)	1.12 (0.89-1.41)	1401	1.06 (0.98-1.15)	1.02 (0.93-1.11)	1.04 (0.95-1.13)	1.04 (0.96-1.14)
100-105	161	1.05 (0.84-1.31)	1.18 (0.92-1.51)	1.01 (0.81-1.27)	1.28 (1.00-1.64)	1321	1.09 (1.00-1.18)	1.01 (0.92-1.11)	1.06 (0.97-1.15)	1.06 (0.96-1.16)
≥105	132	0.90 (0.71-1.14)	1.16 (0.85-1.58)	0.87 (0.68-1.10)	1.33 (0.98-1.80)	1452	1.17 (1.07-1.27)	1.03 (0.92-1.15)	1.13 (1.03-1.23)	1.11 (0.99-1.24)
P trend		*0.0743*	*0.4029*	*0.031*	*0.554*		*0.0007*	*0.8546*	0.0146	*0.2147*
Body shape	**Cases**	**Model 1**		**Model 3**	**Model 4**	**Cases**	**Model 1**		**Model 3**	**Model 4**
Waist<79 cm and hip<98 cm	347	1		1	1	2055	1		1	1
Waist<79 cm and hip≥98 cm	116	1.15 (0.93-1.42)		1.12 (0.90-1.39)	1.25 (1.01-1.56)	582	0.98 (0.90-1.08)		0.96 (0.88-1.05)	0.96 (0.88-1.06)
Waist≥79 cm and hip<98 cm	86	0.91 (0.71-1.15)		0.90 (0.71-1.14)	0.98 (0.77-1.25)	676	1.04 (0.95-1.13)		1.04 (0.95-1.13)	1.02 (0.93-1.12)
Waist≥79 cm and hip≥98 cm	249	0.87 (0.73-1.02)		0.85 (0.71-1.00)	1.09 (0.87-1.35)	2707	1.11 (1.04-1.17)		1.08 (1.02-1.15)	1.05 (0.98-1.13)

Model 1: Adjusted for smoking, education, diabetes, alcohol intake ,previous history of coronary heart disease, physical activity, dietary intake, use of oral contraceptives and use of hormone replacement therapy (only for post-menopausal women).
Model 2: Model 1 further adjusted for hip circumference for the study on waist circumference and for waist circumference for the study on hip circumference.
Model 3: Model 1 further adjusted for adult height
Model 4: Model 1 further adjusted for BMI.

Table 4. Hazard ratios (95% CI) for all cancers according to birth length and weight in pre- and post-menopausal women in the E3N cohort, 1995-2008.

	Hazard Ratio (95% CI)									
Cancer	**Pre-menopausal women**					**Post-menopausal women**				
Birth weight	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Small	90	0.93 (0.74-1.17)	0.94 (0.75-1.19)	0.93 (0.73-1.18)	0.95 (0.75-1.19)	722	0.99 (0.91-1.07)	1.02 (0.94-1.10)	1.02 (0.94-1.11)	1.02 (0.94-1.10)
Medium	498	1	1	1	1	4009	1	1	1	1
High	102	0.87 (0.70-1.08)	0.87 (0.70-1.08)	0.89 (0.71-1.10)	0.88 (0.71-1.10)	721	1.06 (0.98-1.15)	1.04 (0.96-1.13)	1.02 (0.94-1.10)	1.03 (0.95-1.12)
Birth length	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Cases**	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Small	78	1.07 (0.84-1.37)	1.13 (0.88-1.45)	1.04 (0.80-1.35)	1.10 (0.86-1.42)	520	0.90 (0.82-0.98)	0.95 (0.86-1.04)	0.95 (0.86-1.04)	0.95 (0.86-1.05)
Medium	498	1	1	1	1	4024	1	1	1	1
Long	65	1.05 (0.81-1.37)	0.99 (0.75-1.30)	1.01 (0.77-1.34)	1.02 (0.78-1.34)	437	1.18 (1.07-1.30)	1.11 (1.00-1.23)	1.08 (0.97-1.20)	1.10 (0.99-1.22)

Model 1: Adjusted for smoking, education, diabetes, alcohol intake, previous history of coronary heart disease, physical activity, dietary intake, use of oral contraceptives and use of hormone replacement therapy (only for post-menopausal women).
Model 2: Model 1 further adjusted for adult height
Model 3: Model 1 further adjusted for adult height and waist circumference
Model 4: Model 1 further adjusted for BMI.