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PREDICTED BASAL METABOLIC RATE AND CANCER RISK IN THE EUROPEAN PROSPECTIVE INVESTIGATION INTO CANCER AND NUTRITION (EPIC)

Nathalie Kliemann[1], Neil Murphy[1], Vivian Viallon[1], Heinz Freisling[1], Konstantinos K. Tsilidis[2,3], Sabina Rinaldi[1], Francesca Romana Mancini[4,5], Guy Fagherazzi[4,5], Marie-Christine Boutron-Ruault[4,5], Heiner Boeing[6], Matthias B. Schulze[7,8], Giovanna Masala[9], Vittorio Krogh[10], Carlotta Sacerdote[11], Maria Santucci de Magistris[12], Bas Bueno-de-Mesquita[2,13-15], Elisabete Weiderpass[1,16], Tilman Kühn[17], Rudolf Kaaks[17], Paula Jakszyn[18,19], Daniel Redondo-Sánchez[20-22], Pilar Amiano[20,23], Maria-Dolores Chirlaque[20,24], Aurelio Barricarte Gurrea[20,25-26], Ulrica Ericson[27], Isabel Drake[27], Therese Haugdahl Nøst[16], Dagfinn Aune[2,28-29], Anne M. May[30], Anne Tjønneland[31], Christina Catherine Dahm[32], Kim Overvad[32-33], Rosario Tumino[34], Jose Ramón Quirós[35], Antonia Trichopoulou[36], Anna Karakatsani[36-37], Carlo La Vecchia[36,38], Lena Maria Nilsson[39], Elio Riboli[2], Inge Huybrechts[1], Marc J. Gunter[1]

[1]International Agency for Research on Cancer, 150 Albert Thomas, 69372, Lyon Cedex 08, France

[2]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, W2 1PG, UK

[3]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

[4]CESP, Faculté de médecine, Université Paris-Sud; Faculté de médecine, Université de Versailles St-Quentin En-Yvelines ; INSERM, Université Paris-Saclay, 94805, Villejuif, France

[5]Gustave Roussy, F-94805, Villejuif, France

[6]Department of Epidemiology, German Institute of Human Nutrition Potsdam, Rehbruecke, 14558, Germany

[7]Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam, Rehbruecke, Nuthetal, Germany

[8]Institute of Nutrition Science, University of Potsdam, Nuthetal, Germany

[9]Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network - ISPRO, 50139, Florence, Italy

[10]Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano,Via Venezian,20133 Milano, Italy

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[11]Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, 10126, Italy

[12]AOU Federico II Naples, 80131, Italy

[13]Department for Determinants of Chronic Diseases (DCD), National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands

[14]Department of Gastroenterology and Hepatology, University Medical Centre, Utrecht, The Netherlands.

[15]Department of Social & Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[16] Department of Community Medicine, UiT the Arctic University of Norway, Postal address: PO Box 6050 Langnes, N-9037 Tromsø, Norway

[17]Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), 69120, Heidelberg, Germany

[18]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology- IDIBELL, L'Hospitalet de Llobregat, 08907, Barcelona, Spain

[19]Facultat Ciències Salut Blanquerna, Universitat Ramon Llull, Barcelona, Spain.

[20]CIBER Epidemiology and Public Health CIBERESP, Madrid, Spain

[21]Andalusian School of Public Health (EASP), 18011, Granada, Spain

[22]Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA). Universidad de Granada. Granada, Spain

[23]Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian; Gipuzkoa, 20014, Spain

[24]Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, 30008, Spain

[25]Navarra Public Health Institute, 31008, Pamplona, Spain

[26]Navarra Institute for Health Research (IdiSNA) Pamplona, Spain

[27]Department of Clinical Sciences, Lund University, SE-221 00, Malmö, Sweden

[28]Department of Nutrition, Bjørknes University College, Oslo, Norway

[29]Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University,Hospital, Oslo, Norway

[30]Department of Epidemiology, Julius Center Research Program Cancer, UMC Utrecht, 3508, The Nethderlands

[31]Diet, Genes and Environment, Danish Cancer Society Research Center, København, 2100, Denmark

[32]Department of Public Health, Aarhus University, Aarhus, 8000, Denmark

[33]Department of Cardiology, Aalborg University Hospital

[34]Cancer Registry and Histopathology Department, Azienda Sanitaria Provinciale (ASP) Ragusa, 97100, Italy

[35]Public Health Directorate, 33005, Asturias, Spain

[36]Hellenic Health Foundation, GR-115 27, Athens, Greece

[37]Pulmonary Medicine Department, School of Medicine, National and Kapodistrian University of Athens, "ATTIKON" University Hospital, Haidari, Greece

[38]Department of Clinical Sciences and Community Health Università degli Studi di Milano, Italy

[39]Public health and clinical medicine, Sustainable health, Umeå University, SE-901 87, Sweden

CORRESPONDING AUTHOR

Dr Nathalie Kliemann, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008 Lyon, France. Tel: +33 472 738 919 Email: kliemannn@fellows.iarc.fr

SHORT TITLE

Predicted Basal Metabolic Rate and Cancer Risk

KEY WORDS

Basal metabolic rate; cancer; obesity; metabolic disorder

LIST OF ABBREVIATIONS

Basal metabolic rate (BMR); European Prospective Investigation into Cancer and Nutrition (EPIC); International Agency for Research on Cancer (IARC); World Cancer Research Fund International (WCRF); Type 2 diabetes (T2D); body mass index (BMI); food frequency questionnaires (FFQ); hazard ratios (HRs); 95% confidence intervals (CIs) and reactive oxygen species (ROS).

ARTICLE CATEGORY

Cancer Epidemiology

NOVELITY AND IMPACT

In this multi-country prospective cohort analysis, higher predicted BMR was associated with greater risk for most cancers that have been linked with obesity. Importantly, among normal-weight individuals (BMI<25kg/m^2), BMR was positively associated with cancers of the colon, pancreas, thyroid, esophageal adenocarcinoma, postmenopausal breast, and endometrium. These results suggest that BMR may identify subgroups of the population who are at greater risk of these malignancies that would not have otherwise been identified solely by BMI.

ABSTRACT

Emerging evidence suggests that a metabolic profile associated with obesity may be a more relevant risk factor for some cancers than adiposity *per se*. Basal metabolic rate (BMR) is an indicator of overall body metabolism and may be a proxy for the impact of a specific metabolic profile on cancer risk. Therefore, we investigated the association of estimated BMR with incidence of 13 obesity-related cancers in the European Prospective Investigation into Cancer and Nutrition. Estimated BMR at baseline was calculated using the WHO/FAO/UNU equations and the relationships between BMR and cancer risk were investigated using multivariable Cox proportional hazards regression models. A total of 141,295 men and 317,613 women, with a mean follow-up of 14 years were included in the analysis. Overall, higher BMR was associated with a greater risk for most cancers that have been linked with obesity. However, among normal weight participants, higher BMR was associated with elevated risks of esophageal adenocarcinoma (Hazard Ratio per 1-standard deviation change in BMR [$HR_{1\text{-}sd}$]: 2.46; 95%CI 1.20; 5.03), and distal colon cancer ($HR_{1\text{-}sd}$: 1.33; 95%CI 1.001; 1.77) among

men, and with proximal colon ($HR_{1\text{-}sd}$: 1.16; 95%CI 1.01; 1.35), pancreatic ($HR_{1\text{-}sd}$: 1.37; 95%CI 1.13; 1.66), thyroid ($HR_{1\text{-}sd}$: 1.65; 95%CI 1.33; 2.05), postmenopausal breast ($HR_{1\text{-}sd}$: 1.17; 95%CI 1.11; 1.22), and endometrial ($HR_{1\text{-}sd}$: 1.20; 95%CI 1.03; 1.40) cancers in women. These results indicate that higher BMR may be an indicator of a metabolic phenotype associated with risk of certain cancer types, and may be a useful predictor of cancer risk independent of body fatness.

INTRODUCTION

There is growing consensus that obesity and related metabolic disorders such as Type 2 diabetes (T2D) represent important risk factors for a significant number of cancers. According to a recent report by the International Agency for Research on Cancer (IARC), there is sufficient evidence for obesity to be classified as a causal risk factor for cancers of the esophagus (adenocarcinoma), stomach cardia, colorectum, liver, gallbladder, pancreas, breast (postmenopausal), corpus uteri, ovary, kidney, meningioma, thyroid and multiple myeloma (1), while T2D is an established risk factor for cancers of the colorectum, pancreas, liver, gallbladder, breast, and corpus uteri (2). It has been predicted that at least 5.7 % (approximately 804,100 cases) of the global cancer burden in 2012 could be attributed to high body mass index (BMI) and T2D combined (3).

Emerging evidence suggests that metabolic factors which typically accompany obesity, such as insulin resistance and hyperinsulinaemia, may be more relevant risk factors for some cancers than adiposity *per se*. For example, in analyses conducted within the European Prospective Investigation into Cancer and Nutrition (EPIC) and the Women's Health Initiative (WHI), participants with higher insulin levels were at greater risk of developing colorectal and breast cancer, compared to those with normal insulin levels, regardless of body fatness (4-7). These studies indicate that metabolic factors such as hyperinsulinemia are an important determinant of some common cancers, independent of overall adiposity.

Basal metabolic rate (BMR) is defined as the daily rate of energy metabolism required to preserve the integrity of vital functions in both waking and resting states (8) and represents 35 to 70% of the total energy requirement of an individual. It has been shown that BMR is higher in younger age, in males, and in individuals with greater height, weight and lean body mass (9). BMR has also been shown to be positively associated with pro-inflammatory status among both normal weight and overweight individuals (10), suggesting it may be a marker of metabolic health, independent of adiposity. Consistent with this, in a cohort study of elderly individuals, higher BMR was found to be associated with greater mortality risk, independent of body mass index (BMI) (11). Similarly, a cohort study of Pima Indians found that every 100 kcal increase in daily energy expenditure was associated with 29% higher risk of natural death, regardless of participants' body weight (12). To date, only one study has investigated the association between BMR and cancer risk, and specifically breast cancer, using data from the National Health and Nutrition Examination Survey (NHANES) in the United States. That study found that postmenopausal women in the upper quintile for BMR had significantly greater breast cancer risk compared to those in the lower quintile (13). However, it is currently unknown if BMR is associated with risk of other cancers and whether these relationships are independent of adiposity.

We therefore conducted a comprehensive investigation of predicted BMR and its association with the risk of 13 cancers in the European Prospective Investigation into Cancer (EPIC) a prospective cohort of over 520,000 participants with baseline data on BMR. The large number of recorded incident cancer cases afforded sufficient statistical power to investigate the BMR and cancer relationships according to sex and by strata of body habitus (normal weight and overweight).

MATERIALS AND METHODS

Study Participants

The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing multicentre prospective cohort study, designed to investigate the associations between diet, lifestyle, genetic and environmental factors and various types of cancer. A detailed description of this cohort study has been published elsewhere (14, 15). Briefly, a total of 521,324 participants (~70% female) were recruited between 1992 and 2000 from 23 centers across ten European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). All study participants provided written informed consent. Ethical approval for the EPIC study was obtained from the review boards of the International Agency for Research on Cancer and local participating centres: National Committee on Health Research Ethics (Denmark); Comité de Protection des Personnes (France); Ethics Committee of the Heidelberg University Medical School (Germany); Ethikkommission der Landesärztekammer Brandenburg Cottbus (Germany); University of Athens Medical School (Greece) Comitato Etico Indipendente, Fondazione IRCCS Istituto Nazionale dei Tumori (Italy); Human Genetics Foundation Torino Ethics Committee (Italy); Medical Ethical Committee (METC) of the University Medical Center Utrecht (the Netherlands); Regional Ethical Committee for Northern Norway and the Norwegian Data Inspectorate (Norway); Comité de Ética de Investigación Clínica (Spain); Ethics Committee of Lund University (Sweden); Umea Regional Ethical Review Board (Sweden); Norwich District Ethics Committee (UK); Scotland A Research Ethics Committee (UK); and the Imperial College Research Ethics Committee (UK). The current study included participants with information at baseline on sex, age, weight, and height, which were used to compute the basal metabolic rate (BMR). Participants were excluded if they were: pregnant at baseline (n=547); had cancer at recruitment (n=25,184); had missing follow-up information (n=4,148); had missing baseline questionnaire data (n=6,259); self-reported thyroid disease as this may affect individuals' BMR (n=16,705); or were within the extreme ranking (top and bottom 1%) of the ratio energy intake/energy requirement (n=9,573). This cut-off point for the ratio of energy

intake/energy requirement is a routine exclusion made on the EPIC baseline questionnaire on all EPIC analyses. A more stringent cut-off point (top and bottom 5%) was performed with no change in the study results (data not shown).

Follow-up for Cancer Incidence

Incident cancer cases were identified using cancer registries in Norway, Sweden, United Kingdom, Spain, Italy, the Netherlands, and Denmark. For other countries, such as France, Germany and Greece, incident cancer cases were identified during follow-up from a combination of sources including cancer and pathology centres, health insurance records and active follow-up of study subjects. All countries followed a detailed protocol for the collection and standardization of clinical and pathological data on each cancer site (16-19). The end of follow-up was established as the latest date of follow-up for cancer incidence, death or end of follow-up, whichever came first. Censoring dates for complete follow-up from cancer registries were between December 2009 and December 2013. Cancer cases were identified using the 10th Revision of the International Classification of Diseases (ICD-10) and the 2nd Revision of the International Classification of Diseases for Oncology (ICDO-2). In the current analysis we focused on cancers judged to be related to obesity by IARC and WCRF (1, 20) : esophageal adenocarcinoma (C150-159), stomach cardia (C160), colon (C180-189), rectal (C199-209), liver: hepatocellular carcinoma (220-221), gallbladder (C239), pancreas (C250-259), breast: premenopausal and postmenopausal (C500-509), endometrium (C540-549), ovarian (C569), kidney (C649), meningioma (C700-709), thyroid (C739) and multiple myeloma (C420-424). Whenever possible, morphology information was used to classify the malignant tumours according to histological type, as for example, esophageal adenocarcinoma and hepatocellular carcinoma.

Baseline Characteristics

At baseline, information on lifestyle, dietary intake and medical information as well as demographics and anthropometric data were collected. Lifestyle and medical history questionnaires were used to obtain information on education, smoking status and intensity, alcohol consumption, diabetes and women's health (menopausal status, oral contraceptive use, hormone replacement use, age at menarche and age at first full-term pregnancy). Physical activity levels were estimated using a questionnaire focused on past-year physical activity in occupational, leisure and household domains and classified according to the validated Cambridge physical activity index (21). Validated country/centre-specific dietary questionnaires were used to obtain information on dietary intake (energy, dietary fibre, fish and shellfish, meat and processed meat intake). The types of dietary questionnaires used varied according to the study centre, including semi-quantitative food frequency questionnaires (FFQ) with or without an estimation of individual average portion size and diet history questionnaires combining a FFQ and 7-day dietary recalls (15). Body weight and height were measured in all centres, except for Oxford, France and Norway where these were self- reported. Anthropometric characteristics were measured by trained observers using standardized methods (15). Body weight was measured by electronic digital scales, with subjects wearing only light underwear and after emptying the bladder. Height was measured to the nearest 0.1 cm using a flexible anthropometers (22). Assessed weight and height were used to calculate BMI defined as weight in kilograms divided by height in metres squared (kg/m^2).

Assessment of predicted Basal Metabolic Rate

Predicted BMR at baseline was calculated for each participant using the WHO/FAO/UNU (23) equations, which are based on Schofield equations (24). This method calculates BMR using gender and age-specific equations (18 to 30 years; 31 to 60 years and >60 years) as shown in **S1 Table**. The equations also take into account an individuals' weight and height. This method is one of the most

frequently used to assess BMR in dietary studies and according to the experts of the European Food Safety Authority (EFSA), it can be considered as equally valid as those more recently developed (25). For comparison, BMR was also assessed using other methods including the Oxford (8), Harris-Benedict (26) and Mifflin St Jeor (27) equations that also use sex, age, weight and height to predicted BMR (**S1 Table**).

Statistical Analysis

Pearson correlation coefficients between BMR defined by WHO/FAO/UNU and the other BMR equations were derived. The Pearson correlation coefficients between BMR, BMI, weight and height were also assessed. The relationships between BMR and BMI with cancer risk were investigated using multivariable Cox proportional hazards regression models (Hazard ratio [HR] and 95% confidence intervals [95%CI]). Time at entry was age at recruitment and exit time was age at cancer diagnosis, end of follow-up, lost to follow-up or death, whichever came first. Models were stratified by country and age at recruitment (in 1-year categories) to control for age and country-specific effects. Sex-specific BMR and BMI continuous variables were normalised to 1-standard deviation, in order to allow the comparison of the associations of these exposures with cancer risk. Multivariable models were adjusted for other cancer risk factors, namely: education (none; primary school; technical/professional school; secondary school; and longer education), physical activity index (inactive; moderately inactive; moderately active; and active), smoking (never; former; and smoker), alcohol consumption (g/d), dietary intakes related to cancer risk (energy, dietary fibre, fish and shellfish, meat and processed meat intake), self-reported diabetes at recruitment (yes; no), and menopausal hormone therapy (never; ever), for women only. Further adjustment for other risk factors was also tested such as dairy intake of calcium (g/d), but since no difference was observed in the HRs, these were excluded from the final models. For female-specific cancer sites (e.g. cancers of the

reproductive system) the models were further adjusted for menopausal status (premenopausal; postmenopausal; perimenopausal; and surgical postmenopausal) oral contraceptive use (never; ever), age at menarche (y) and age at first full-term pregnancy (y). Chi-squared tests were performed to evaluate whether the parameters of BMR and BMI for each cancer were significantly different (p-heterogeneity). In an attempt to investigate the relationship between BMR and cancer risk, independent of BMI, BMR residuals were computed from a linear regression of BMR on BMI, height, age, country and sex. BMR residuals were normalised to 1-standard deviation and investigated in relation to cancer risk in multivariable Cox proportional hazards regression models, which were further adjusted for BMI. We also examined the relationship between BMR and cancer risk among normal weight (BMI<25 kg/m^2) and overweight/obese groups (BMI≥25 kg/m^2), and assessed heterogeneity between these subgroups and BMR by using interaction terms (multiplicative scale); the statistical significance of the cross-product terms was evaluated using the likelihood ratio test. This stratified analysis was also repeated using BMR residuals.

All analyses were repeated separately according to menopausal status for female reproductive cancers. Women contributed person-time to the 'premenopausal model' until their age of menopause onset and from their age of menopause onwards to the 'postmenopausal model'. Menopause age was collected at baseline for postmenopausal women. If missing, and if women were premenopausal at baseline, then menopause age was set as 55 years. Sensitivity analyses were performed excluding participants who self-reported chronic diseases (heart disease, diabetes, and stroke) and who self-reported weight and height at recruitment. The influence of preclinical disease on the results was assessed by excluding participants diagnosed within the first 2 years of follow-up. Statistical tests used in the analysis were all two-sided, and a p-value of <0.05 was considered as statistically significant. Statistical analyses were conducted using Stata v11.0 and the figures were constructed using R.

Data Availability

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. The primary responsibility for accessing the data belongs to the EPIC centres that provided them. The use of a random sample of anonymised data from the EPIC study can be requested by contacting epic@iarc.fr. The request will then be passed to members of the EPIC Steering Committee for deliberation.

RESULTS

A total of 141,295 men and 317,613 women with a mean age of 52 and 50 years at baseline, respectively, were included in the analysis. The mean follow-up time was 14 years (SD 4.0). Both male and female participants with higher BMR were taller, had higher BMI and reported greater intake of fish and shellfish and red and processed meat (**Table 1**). Male participants with higher BMR were more likely to report higher caloric and alcohol intake compared to those in the lowest category, while for female participants an opposite trend was observed. Female participants with higher BMR also had lower attained education level; earlier age at menarche and earlier age at first full pregnancy. Predicted BMR calculated using the WHO/FAO/UNU equation was strongly correlated (r>.96) with those derived from the other BMR equations. Correlation coefficients between predicted BMR and BMI were 0.53 among men and 0.77 among women (**S2 Table**).

Association of predicted BMR with Cancer Risk

The hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between BMR and risk for cancers at different anatomical sites, and their comparison with HRs and 95%CIs for the associations of cancer endpoints with BMI, are displayed in **Figures 1 (men) and 2 (women).** Results for colon cancer showed that a one standard deviation increase in BMR was associated with 29% (95%CI 1.21; 1.38) higher risk for men and 8% (95%CI 1.03; 1.13) higher risk for women (similar patterns of results were observed for proximal and distal colon cancers). For pancreatic cancer, a one standard deviation increase in BMR was associated with 13% (95%CI 1.01; 1.26) and 17% (95%CI 1.08; 1.26) higher risk in men and women, respectively. Similarly, a one standard deviation increase in BMR was associated with an increased risk for kidney cancer in men ($HR_{1\text{-}sd}$ 1.40; 95%CI 1.25; 1.55) and in women ($HR_{1\text{-}sd}$ 1.19; 95%CI 1.08; 1.30). For gallbladder cancer, one standard deviation increase in BMR was associated with 98% (95%CI 1.18; 3.32) higher risk in men and 31% (95%CI 1.07; 1.61) higher risk in women. BMR was also positively associated with risks of stomach cardia ($HR_{1\text{-}sd}$: 1.34, 95%CI 1.08; 1.67), meningioma ($HR_{1\text{-}sd}$: 1.21, 95%CI 1.08; 1.35) and thyroid ($HR_{1\text{-}sd}$: 1.17, 95%CI 1.07; 1.28) cancers among women. For men, BMR was positively associated with risks of HCC ($HR_{1\text{-}sd}$: 1.38; 95%CI 1.13; 1.68), esophageal adenocarcinoma ($HR_{1\text{-}sd}$: 1.49; 95%CI 1.21; 1.83), and multiple myeloma ($HR_{1\text{-}sd}$: 1.15; 95%CI 1.05; 1.26). BMR remained statistically significant associated with most cancer sites when the multivariable models used BMR residuals and were further adjusted for BMI (**Table 2**).

For female-specific cancers, one standard deviation increment in BMR was associated with a 8% (95%CI 1.08; 1.10) higher risk of breast cancer, 39% (95%CI 1.33; 1.47) higher risk of endometrial cancer, and 8% (95%CI 1.01; 1.15) higher risk of ovarian cancer. When these analyses were stratified by menopausal status, the associations were only evident among postmenopausal women (**S3 Table**).

The associations between BMI and risks of individual cancers were generally similar to those found for BMR (**Figures 1 and 2**). However, for breast cancer, compared to BMI, BMR was more strongly associated with risk (p-heterogeneity=0.014) (**Figure 2**). For cancers of the proximal colon (women only), stomach cardia, and thyroid (both men only) positive relationships were only found with BMR, but not with BMI; however, the heterogeneity did not meet the threshold of significance (p-heterogeneity>0.05) (**Figures 1 and 2**).

BMR and Cancer Risk in Normal Weight and Overweight/Obese Groups

Among normal weight participants (BMI<25 kg/m^2), higher BMR was associated with elevated risks of esophageal adenocarcinoma ($HR_{1\text{-}sd}$: 2.46; 95%CI 1.20; 2.03), and distal colon cancer ($HR_{1\text{-}sd}$: 1.33; 95%CI 1.001; 1.77) among men, and of proximal colon ($HR_{1\text{-}sd}$: 1.16; 95%CI 1.01; 1.35), pancreatic ($HR_{1\text{-}sd}$: 1.37; 95%CI 1.13; 1.66), thyroid ($HR_{1\text{-}sd}$: 1.65; 95%CI 1.33; 2.05), breast ($HR_{1\text{-}sd}$: 1.17; 95%CI 1.11; 1.22), and endometrial ($HR_{1\text{-}sd}$: 1.20; 95%CI 1.03; 1.40) cancers among women (Table 2). For overweight/obese men, BMR was positively related to risks of all cancers, although the positive relationships observed for stomach cardia, gallbladder, meningioma, thyroid and rectal cancers did not reach the threshold of significance. For overweight/obese women, BMR was positively and significantly associated with pancreatic ($HR_{1\text{-}sd}$: 1.17; 95%CI 1.05; 1.31), kidney ($HR_{1\text{-}sd}$: 1.16; 95%CI 1.02; 1.32), breast ($HR_{1\text{-}sd}$: 1.07; 95%CI 1.03; 1.11), endometrial ($HR_{1\text{-}sd}$: 1.41; 95%CI 1.31; 1.51), and ovarian ($HR_{1\text{-}sd}$: 1.12; 95%CI 1.02; 1.24) cancers (**Table 3).** BMR remained statistically significantly associated with most cancer sites when the stratified analyses were repeated using BMR residuals (**Table 4).** When these analyses were stratified by menopausal status, the associations were only evident among postmenopausal women, even when using BMR residuals (**S4 Table**). For the majority of cancer sites, there was no heterogeneity in the association of BMR with cancer risk among individuals with normal weight or with overweight or obesity. The exception was

for breast cancer, where higher BMR was more strongly associated with breast cancer among women with normal weight compared to those with overweight or obesity (P-heterogeneity=0.002).

Sensitivity analysis

The results were largely unchanged after cancer cases which occurred during the first 2 years of follow-up were excluded (**S5 Tables**). Also, sensitivity analyses excluding participants who self-reported chronic diseases (**S6 Tables**) and who self-reported weight and height (**S7 Tables**) at recruitment showed similar results.

DISCUSSION

In this multi-country prospective cohort analysis, higher predicted BMR was associated with greater risk for most cancers that have been linked with obesity. Importantly, among normal-weight individuals (BMI<25kg/m^2), higher BMR was associated with a greater risk of colon, pancreas, thyroid, esophageal adenocarcinoma, postmenopausal breast, and endometrial cancer. These results suggest that BMR may identify subgroups of the population who are at greater risk of these malignancies that would not have otherwise been identified solely by BMI.

The reprogramming of energy metabolism is one of the hallmarks of cancer and metabolic transformation is a key event in tumorigenesis. Markers of metabolic health such as insulin regulation or of adiposity such as waist circumference and BMI are risk factors for a number of different cancers. In this analysis, we found that predicted BMR, which reflects whole body energy metabolism, was associated with the development of specific cancers, even among lean individuals. In terms of potential biological mechanisms, individuals with higher BMR require greater cellular energy generation to meet their higher energy and metabolic requirements. Enhanced aerobic glycolysis may lead to a greater reactive oxygen species (ROS) generation, a by-product of cellular

respiration. Although ROS production and detoxification are usually well balanced, a shift in this equilibrium may lead to ROS in excess promoting oxidative stress (28) and the accumulation of oncogenic DNA defects as well as the activation of oncogenic signalling pathways (29). In fact, a recent review suggested that higher BMR could increase cancer risk by means of higher oxidative stress and mutational rates (30). Increased ROS has also been linked to many metabolic alterations, such as insulin resistance (31), decreases in adiponectin and increased expression of pro-inflammatory cytokines including TNFα and IL-6 (32). In line with this, BMR has been positively associated with levels of insulin and Type 2 diabetes (33-35), although conflicting results have also been found (36, 37). Previous studies have shown that these metabolic alterations can drive cancer development in both normal weight (4-7) and overweight individuals (33-35), which are in agreement with the results from the current study, showing that BMR was associated with cancer risk independent of BMI.

The potential link between BMR and cancer may also explain why taller individuals have higher risk of certain cancers (38-41). Taller individuals have a greater requirement of energy metabolism due to a higher number of cells and organ mass. Although the underlying biological mechanisms are still not completely elucidated, it is suggested that the number of cells may influence the effect of height on cancer risk, as it would also increase the opportunities for mutations and malignant tumour development (42, 43). Higher exposure to growth hormones (GH) and insulin-like growth factor-1 (IGF-1) during early growth, which might be activated by overnutrition during different stages of child development, may also be relevant (44-47), and it may differ by anatomical subsites (39).

To our knowledge, this is the first investigation on the association between predicted measures of BMR and multiple cancers in a large-scale prospective cohort setting. The long term follow-up and high number of incident cancer cases recorded allowed us to investigate the BMR and cancer associations by sex and body size groups. However, some limitations of the current study should also

be considered. First, BMR was only predicted and was assessed using WHO/FAO/UNU equations, which may overestimate actual BMR (8), particularly among overweight and obese individuals (48). This may occur as BMR equations take into account total body mass and do not make a distinction between lean and fat mass which differ metabolically. However, in our analysis BMR calculated using the WHO/FAO/UNU equation was strongly correlated with BMR predicted by Mufflin St Jean equation, which has been considered the most accurate for overweight and obese individuals (49). Although indirect calorimetry may be a more reliable tool to measure BMR, it is expensive compared to predictive equations and not realistic for large-scale population-based studies (9, 50). It is also important to note that only predicted BMR at baseline has been assessed in EPIC, while multiple measurements over time may allow a more precise assessment of the impact of BMR on cancer risk. Furthermore, the models were not adjusted for body fat-free mass, a factor that influences BMR (9), as this variable was not available. Another potential limitation is the quantity of missing data for self-reported thyroid disease in EPIC, which is also an important factor that affects an individual's BMR. However, given that only ~10% of the European population suffers from clinically manifest thyroid disease (51), it is unlikely that failure to capture this information would have substantially affected our results.

Further, as BMR is a composite function of age, sex, height and weight, which are well known risk factors for cancer, it is possible that BMR may be capturing part of the effect of these variables on cancer. In an attempt to disentangle the association between predicted BMR and BMI, and to explore whether BMR captures additional information beyond BMI that may be relevant for cancer prediction, we repeated the analysis using BMR residuals and further adjusted the models by BMI or stratified them by BMI group. The results confirmed an association between BMR and cancer risk beyond adiposity.

In conclusion, higher predicted BMR was associated with most obesity-related malignancies and may be an indicator of a metabolic phenotype associated with cancer risk. Importantly, among normal-weight individuals, higher BMR was related to greater risks of cancers of the colon, pancreas, thyroid, postmenopausal breast, endometrium, and esophageal adenocarcinoma. For these cancer sites, BMR may be a useful predictor of cancer risk regardless of overall adiposity. Further understanding of the role of metabolic dysfunction on cancer risk is needed. Additionally, the replication of these analyses using BMR measured by indirect calorimetry and adjusting for body composition (e.g. fat-mass and fat-free mass) could provide more robust evidence for the association between BMR and cancer risk.

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CONFLICT OF INTEREST

The authors are not aware of any conflicts of interest.

AUTHOR CONTRIBUTIONS

ER is the overall coordinator of the EPIC study, which he conceptualised, designed, and implemented in collaboration with the main investigators in the collaborating centres. All authors contributed to the methodology and investigation (e.g. recruitment and data collection/acquisition), and are responsible for the ongoing follow-up and management of the EPIC cohort: ER, MJG, NK, NM, IH, VV, HF, KKT, SR, FRM, GF; MCBR, HB, MBS, GM, VK, CS, MSM, BBM, EW, TK, RK, PJ, DRS, PA, MDC, ABG, UE, ID, THN, DA, AMM, AT, CCD, KO, RT, JRQ, AT, AK, CLV and LMN. The

analyses were performed by NK with assistance from MJG, NM, IH, VV and HF. This article was written by NK, MJG, NM, IH, VV, HF and KKT, taking into account the comments and suggestions of the other co-authors. All co-authors had the opportunity to comment on the analysis and interpretation of the findings and approved the final version for publication. All authors have read, and confirm that they meet ICMJE criteria for authorship.

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DISCLAIMER

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

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Figure 1. Hazard ratio (HR) and 95% confidence intervals (CI) for cancer risk in relation to Basal Metabolic Rate (BMR) and Body Mass Index (BMI) in men

Note. BMR: 1-standard deviation increase. BMI: 1-standard deviation increase. BMR and BMI estimates were derived from separate models. Cox proportional hazard regression models were stratified by center and age and adjusted for education, physical activity, smoking, alcohol consumption, dietary intake (energy intake, meat intake, fish and shellfish intake and fibre intake), self-reported diabetes at recruitment. *P-value for heterogeneity explored by chi-squared tests.

Figure 2. Hazard ratio (HR) and 95% confidence intervals (CI) for cancer risk in relation to Basal Metabolic Rate (BMR) and Body Mass Index (BMI) in women

Note. BMR: 1-standard deviation increase. BMI: 1-standard deviation increase. BMR and BMI estimates were derived from separate models. Cox proportional hazard regression models were stratified by center and age and adjusted for education, physical activity, smoking, alcohol consumption, dietary intake (energy intake, meat intake, fish and shellfish intake and fibre intake), self-reported diabetes at recruitment, and hormonal replacement.**P*-value for heterogeneity explored by chi-squared tests.

Table 1. Baseline characteristics of EPIC participants by tertiles of BMR

	All (N=458,908)	Men (N=141,295)			Women (N=317,613)		
		Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
	N(%) or Mean±SD	N(%) or Mean±SD	N(%) or Mean±SD	N(%) or Mean±SD	N(%) or Mean±SD	N(%) or Mean±SD	N(%) or Mean±SD
Basal Metabolic Rate, kcal/d	1507±230.1	1591±117.1	1795±37.1	1972±104.3	1276±50.3	1372±22.9	1503±5.9
Age at recruitment, y	51±9.9	57±10.9	50±8.8	49±8.3	52±10.7	50±9.1	50±9.3
BMI, kg/m^2	25.4±4.2	24.7±3.3	25.6±2.5	29.1±3.4	21.8±2.7	24.1±2.5	28.9±4.3
Height, m	1.66±.09	1.70±.06	1.74±.06	1.78±.06	1.59±.05	1.63±.06	1.65±.07
Caloric intake, kcal/d	2076±620.9	2310±622.9	2433±658.4	2485±692.2	1938±530.6	1931±534.8	1913.±550.4
Total dietary fibre, g/d	23±7.7	23±8.3	24±8.4	24±8.4	22±7.5	22±7.4	22±7.3
Fish and shellfish, g/d	37±35.7	35±32.5	35±33.8	37±34.9	33±31.8	38±37.4	40±39.7
Red & processed meat, g/d	75±51.2	85±56.9	96±59.9	109±64.3	60±41.8	64±41.5	70±43.4
Alcohol, g/d	12±16.9	18±21.5	20±22.2	22±**24.9**	8±11.6	8±11.7	7±11.4
Smoking status							
Never	222,996 (48.6)	15,593(33.1)	16,231 (34.4)	14,765 (31.3)	61,680 (58.2)	57,368 (54.2)	57,359 (54.2)
Current	104,096 (22.7)	13,392 (28.4)	14,213 (30.2)	14,001 (29.7)	20,241 (19.1)	21,321 (20.1)	20,928 (19.7)
Physical activity index							
Inactive	95,451 (20.8)	11,534(24.5)	7,150 (15.2)	7,798 (16.5)	23,703 (22.4)	20,303(19.2)	24,963 (23.6)
Active	83,215 (18.1)	9,856(20.9)	12,413 (26.4)	11,993 (25.5)	14,992 (14.1)	17,507 (16.5)	16,454 (15.5)
Longer education	108,472 (23.9)	10,831 (23.3)	13,741 (29.4)	12,696 (27.1)	28,104 (27.0)	24,890 (23.9)	18,210 (17.4)
Diabetes	11,830 (2.8)	2,236 (5.4)	1,213 (2.7)	1,592 (3.6)	1,815 (1.8)	1,652 (1.7)	3,322(3.4)
Menopausal status							
Premenopausal	111,601 (24.3)	-	-	-	36,088(34.0)	39,936(37.7)	35,577(33.6)
Postmenopausal	136,239 (29.7)	-	-	-	49,725(46.9)	41,521(39.2)	44,993(42.5)
Oral contraceptives							
Never	127,549 (27.8)	-	-	-	44,682(42.1)	39,005(36.9)	43,862(41.4)
Current	181,707 (39.6)	-	-	-	58,630(55.3)	63,940(60.4)	59,137(55.8)
Hormone replacement							

Never	221,453 (48.2)	-	-	-	74,820(70.6)	73,242(69.2)	73,391(69.3)
Current	51,335 (11.1)	-	-	-	17,058(16.1)	17,951(16.9)	16,326(15.4)
Age at menarche, y	13±1.5	-	-	-	13±1.5	13±1.5	13±1.5
Age at first full pregnancy, y	25±4.3	-	-	-	25±4.3	25±4.3	24±4.3

Table 2. Hazard ratio (HR) and 95% confidence intervals (CI) for cancer risk in relation to Basal Metabolic Rate residuals in men and women

Cancer Site	Men	Women
	HR (95%CI)	HR (95%CI)
Esophageal adenocarcinoma	1.12 (0.94; 1.32)	1.05 (0.86; 1.29)
Stomach cardia	1.16 (0.97; 1.37)	1.12 (0.97; 1.28)
Colon	1.10 (1.05; 1.16)	1.05 (1.02; 1.07)
Proximal Colon	1.12 (1.03; 1.21)	1.07 (1.04; 1.12)
Distal Colon	1.13 (1.05; 1.22)	1.02 (0.98; 1.07)
Rectal	0.96 (0.91; 1.03)	0.98 (0.94; 1.02)
HCC[a]	0.88 (0.77; 1.00)	0.95 (0.82; 1.08)
Gallbladder	1.36 (0.94; 1.96)	1.15 (1.01; 1.31)
Pancreas	1.03 (0.95; 1.13)	1.10 (1.05; 1.16)
Kidney	1.11 (1.02; 1.21)	1.01 (0.96; 1.08)
Meningioma	0.84 (0.66; 1.05)	1.03 (0.96; 1.11)
Thyroid	1.50 (1.16; 1.93)	1.13 (1.06; 1.20)
Multiple Myeloma	1.07 (1.00; 1.15)	1.06 (1.02; 1.10)
Breast	-	1.05 (1.03; 1.07)
Endometrium	-	1.04 (1.01; 1.08)
Ovarian	-	1.04 (0.99; 1.08)

Note. BMR residual: 1-standard deviation increase. Models were stratified by center and age and adjusted for education, physical activity, smoking, alcohol consumption, dietary intake (energy intake, meat intake, fish and shellfish intake and fibre intake), self-reported diabetes at recruitment, hormonal replacement (for women only) and BMI. Additional adjustment

for menopause status, oral contraceptive, age at menarche and age at first full-term pregnancy for women-only cancer sites.
[a]Hepatocellular Carcinoma.

Table 3. Hazard ratios (HR) and 95% confidence intervals (CI) for cancer risk in relation to Basal Metabolic Rate (BMR) by body habitus status in men and women

Cancer site	Men			Women		
	Normal weight N or HR (95%CI)	Overweight N or HR (95%CI)	*P**	Normal weight N or HR (95%CI)	Overweight N or HR (95%CI)	*P**
Esophageal adenocarcinoma						
N° subj/cases	46,118/ 32	82,723/ 96		170,760/ 10	119,663/ 22	
BMR	2.46 (1.20; 5.03)	1.36 (1.05; 1.77)	0.094	1.05 (0.39; 2.82)	0.95 (0.60; 1.51)	0.919
Stomach cardia						
N° subj/cases	46,118/ 45	82,723/ 92		170,760/ 27	119,663/ 41	
BMR	1.05 (0.59; 1.86)	1.24 (0.94; 1.65)	0.692	1.69 (.088; 3.24)	1.16 (0.85; 1.59)	0.173
Colon						
N° subj/cases	46,118/382	82,723/ 1,031		170,760/ 1,035	119,663/ 1,051	
BMR	1.19 (0.98; 1.44)	1.30 (1.20; 1.41)	0.919	1.11 (1.00; 1.23)	1.07 (1.00; 1.14)	0.765
Colon Proximal						
N° subj/cases	46,118/160	82,723/ 400		170,760/ 514	119,663/ 499	
BMR	1.19 (0.88; 1.58)	1.37 (1.20; 1.56)	0.375	1.16 (1.01; 1.35)	1.09 (0.99; 1.20)	0.575
Colon Distal						
N° subj/cases	46,118/171	82,723/ 400		170,760/ 418	119,663/ 424	
BMR	1.33 (1.00; 1.77)	1.29 (1.15; 1.46)	0.535	1.05 (0.88; 1.24)	1.05 (0.95; 1.17)	0.743
Rectal						
N° subj/cases	46,118/288	82,723/ 678		170,760/ 506	119,663/ 446	
BMR	0.99 (0.79; 1.23)	1.03 (0.92; 1.14)	0.964	1.10 (0.94; 1.28)	1.004 (0.90; 1.11)	0.606
HCC[a]						
N° subj/cases	46,118/ 34	82,723/ 107		170,760/ 25	119,663/ 39	
BMR	0.95 (0.50; 1.80)	1.48 (1.17; 1.88)	0.260	1.01 (0.52; 1.95)	0.95 (0.66; 1.37)	0.379
Gallbladder						
N° subj/cases	46,118/ 4	82,723/ 18		170,760/ 29	119,663/ 56	
BMR	-[¥]	1.43 (0.76; 2.71)	0.079	1.38 (0.70; 2.70)	1.25 (0.96; 1.65)	0.639
Pancreas						
N° subj/cases	46,118/167	82,723/362		170,760/ 5312	119,663/ 334	
BMR	0.98 (0.73; 1.33)	1.18 (1.03; 1.37)	0.501	1.37 (1.13; 1.66)	1.17 (1.05; 1.31)	0.595
Kidney						
N° subj/cases	46,118/ 130	82,723/ 378		170,760/ 190	119,663/ 244	
BMR	1.21 (0.86; 1.68)	1.42 (1.24; 1.62)	0.455	1.13 (0.88; 1.46)	1.16 (1.02; 1.32)	0.922
Meningioma						
N° subj/cases	46,118/ 22	82,723/ 47		170,760/ 134	119,663/ 184	
BMR	0.27 (0.10; .68)	1.19 (0.77; 1.84)	0.259	1.20 (0.86; 1.67)	1.10 (0.94; 1.29)	0.898
Thyroid						
N° subj/cases	46,118/ 26	82,723/ 60		170,760/ 321	119,663/ 260	
BMR	1.38 (0.63; 3.06)	1.26 (0.87; 1.83)	0.376	1.65 (1.33; 2.05)	1.04 (0.90; 1.20)	0.002
Multiple Myeloma						
N° subj/cases	46,118/ 272	82,723/ 536		170,760/ 586	119,663/ 485	
BMR	1.12 (0.89; 1.41)	1.26 (1.12; 1.41)	0.669	1.07 (0.93; 1.24)	1.08 (0.98; 1.19)	0.743
Breast						
N° subj/cases	-	-		130,681/ 6,196	101,445/4,462	
BMR	-	-		1.17 (1.11; 1.22)	1.07 (1.03; 1.11)	0.002

Endometrium					
N° subj/cases	-	-	130,681/ 553	101,445/ 779	
BMR	-	-	1.20 (1.03; 1.40)	1.41 (1.31; 1.51)	0.123
Ovary					
N° subj/cases	-	-	130,681/ 527	101,445/ 457	
BMR	-	-	1.10 (0.94; 1.29)	1.12 (1.02; 1.24)	0.766

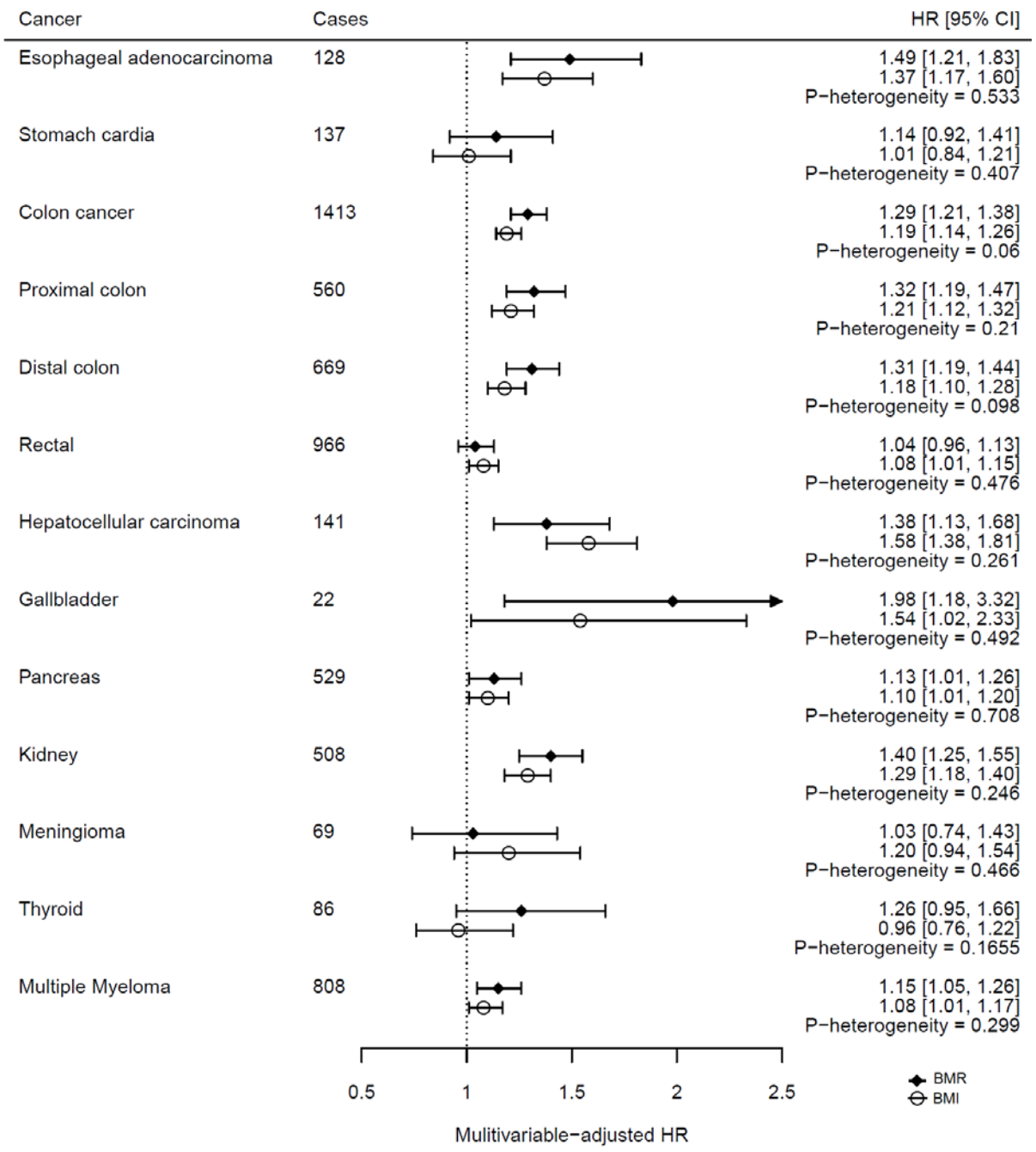
Note. BMR: 1-standard deviation increase. Models were stratified by center and age and adjusted for education, physical activity, smoking, alcohol consumption, dietary intake (energy intake, meat intake, fish and shellfish intake and fibre intake), self-reported diabetes at recruitment, and hormonal replacement (for women only). Additional adjustment for menopause status, oral contraceptive, age at menarche and age at first full-term pregnancy for women-only cancer sites. **P*-value for heterogeneity explored by modelling interaction terms between BMR and BMI group. [a]Hepatocellular Carcinoma. Normal weight= BMI between 18.5 and 24.9 kg/m^2. Overweight= BMI 25 kg/m^2 or over. [¥]No sufficient cases.

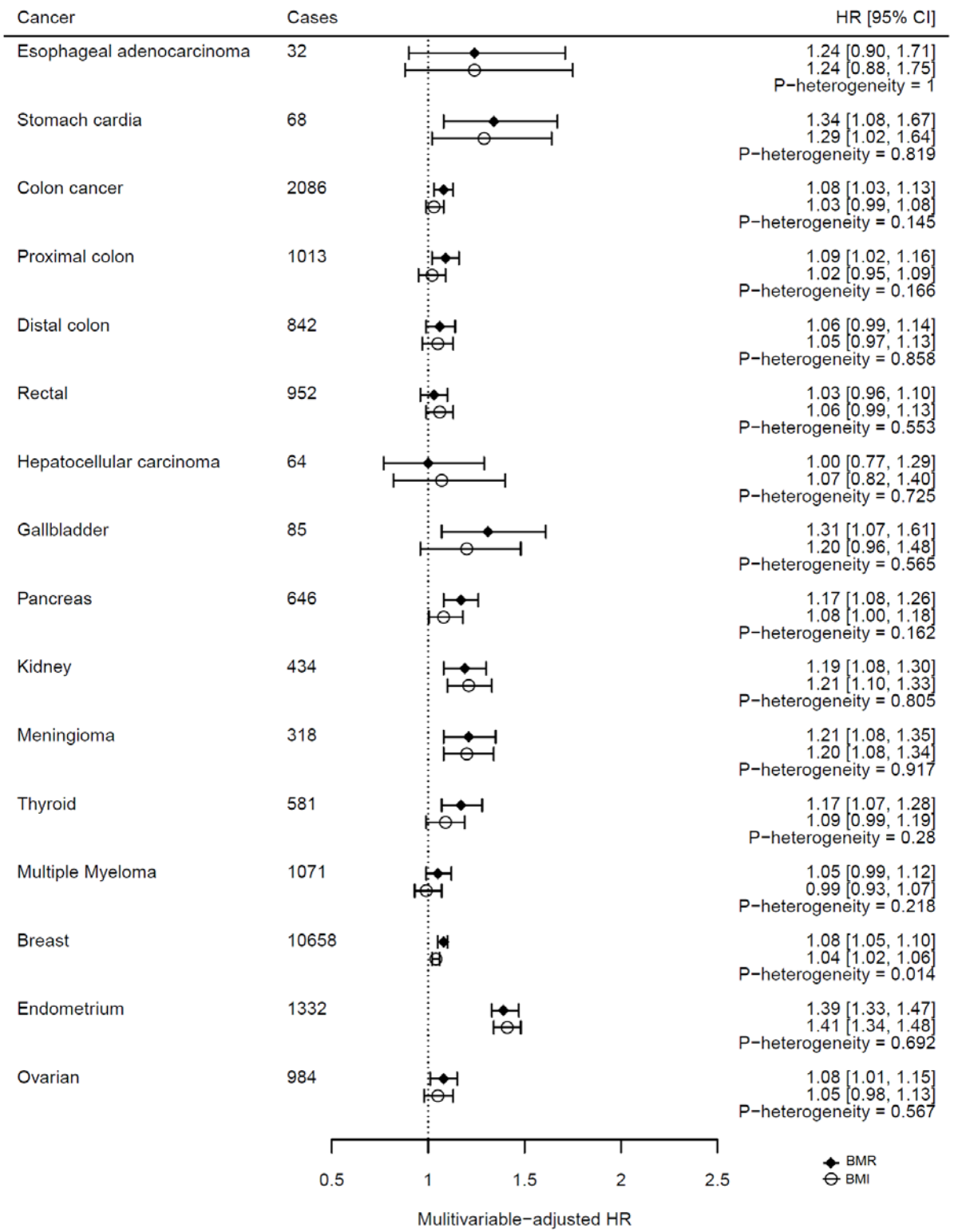
Table 4. Hazard ratio (HR) and 95% confidence intervals (CI) and cancer risk in relation to Basal Metabolic Rate residuals (BMR residuals) by body fatness status in men and women

Cancer site	Men			Women		
	Normal weight N or HR (95%CI)	Overweight N or HR (95%CI)	*P**	Normal weight N or HR (95%CI)	Overweight N or HR (95%CI)	*P**
Esophageal adenocarcinoma						
N° subj/cases	46,118/ 32	82,723/ 96		170,760/ 10	119,663/ 22	
BMR residuals	1.58 (1.10; 2.28)	1.17 (1.02; 1.34)	0.433	1.01 (0.73; 1.41)	0.98 (0.84; 1.14)	0.058
Stomach cardia						
N° subj/cases	46,118/ 45	82,723/ 92		170,760/ 27	119,663/ 41	
BMR residuals	1.03 (0.76; 1.37)	1.11 (0.97; 1.29)	0.622	1.19 (0.96; 1.47)	1.05 (0.94; 1.16)	0.593
Colon						
N° subj/cases	46,118/382	82,723/ 1,031		170,760/ 1,035	119,663/ 1,051	
BMR residuals	1.09 (0.99; 1.20)	1.14 (1.09; 1.19)	0.656	1.03 (1.00; 1.07)	1.02 (1.00; 1.04)	0.577
Colon Proximal						
N° subj/cases	46,118/160	82,723/ 400		170,760/ 514	119,663/ 499	
BMR residuals	1.09 (0.94; 1.26)	1.17 (1.09; 1.25)	0.972	1.05 (1.00; 1.10)	1.03 (0.99; 1.06)	0.223
Colon Distal						
N° subj/cases	46,118/171	82,723/ 400		170,760/ 418	119,663/ 424	
BMR residuals	1.15 (1.00; 1.34)	1.14 (1.07; 1.21)	0.938	1.01 (0.96; 1.07)	1.01 (0.98; 1.05)	0.833
Rectal						
N° subj/cases	46,118/288	82,723/ 678		170,760/ 506	119,663/ 446	
BMR residuals	0.99 (0.88; 1.11)	1.01 (0.96; 1.07)	0.287	1.03 (0.98; 1.08)	1.001 (0.97; 1.03)	0.964
HCC[a]						
N° subj/cases	46,118/ 34	82,723/ 107		170,760/ 25	119,663/ 39	
BMR residuals	0.97 (0.70; 1.35)	1.22 (1.08; 1.38)	0.645	1.003 (0.80; 1.24)	0.98 (0.87; 1.11)	0.476
Gallbladder						
N° subj/cases	46,118/ 4	82,723/ 18		170,760/ 29	119,663/ 56	
BMR residuals	-[¥]	1.20 (0.86; 1.66)	-	1.11 (0.89; 1.38)	1.07 (0.98; 1.18)	0.795
Pancreas						
N° subj/cases	46,118/167	82,723/362		170,760/ 5312	119,663/ 334	
BMR residuals	0.99 (0.85; 1.15)	1.09 (1.01; 1.17)	0.956	1.11 (1.04; 1.18)	1.05 (1.01; 1.09)	0.097
Kidney						
N° subj/cases	46,118/ 130	82,723/ 378		170,760/ 190	119,663/ 244	
BMR residuals	1.10 (0.93; 1.30)	1.19 (1.11; 1.28)	0.688	1.04 (.95; 1.13)	1.05 (1.00; 1.09)	0.374
Meningioma						
N° subj/cases	46,118/ 22	82,723/ 47		170,760/ 134	119,663/ 184	
BMR residuals	0.51 (0.32; 0.82)	1.09 (0.87; 1.36)	0.244	1.06 (0.95; 1.18)	1.03 (0.97; 1.09)	0.067
Thyroid						
N° subj/cases	46,118/ 26	82,723/ 60		170,760/ 321	119,663/ 260	
BMR residuals	1.18 (0.78; 1.77)	1.12 (0.93; 1.36)	0.911	1.18 (1.10; 1.26)	1.01 (0.96; 1.06)	0.413

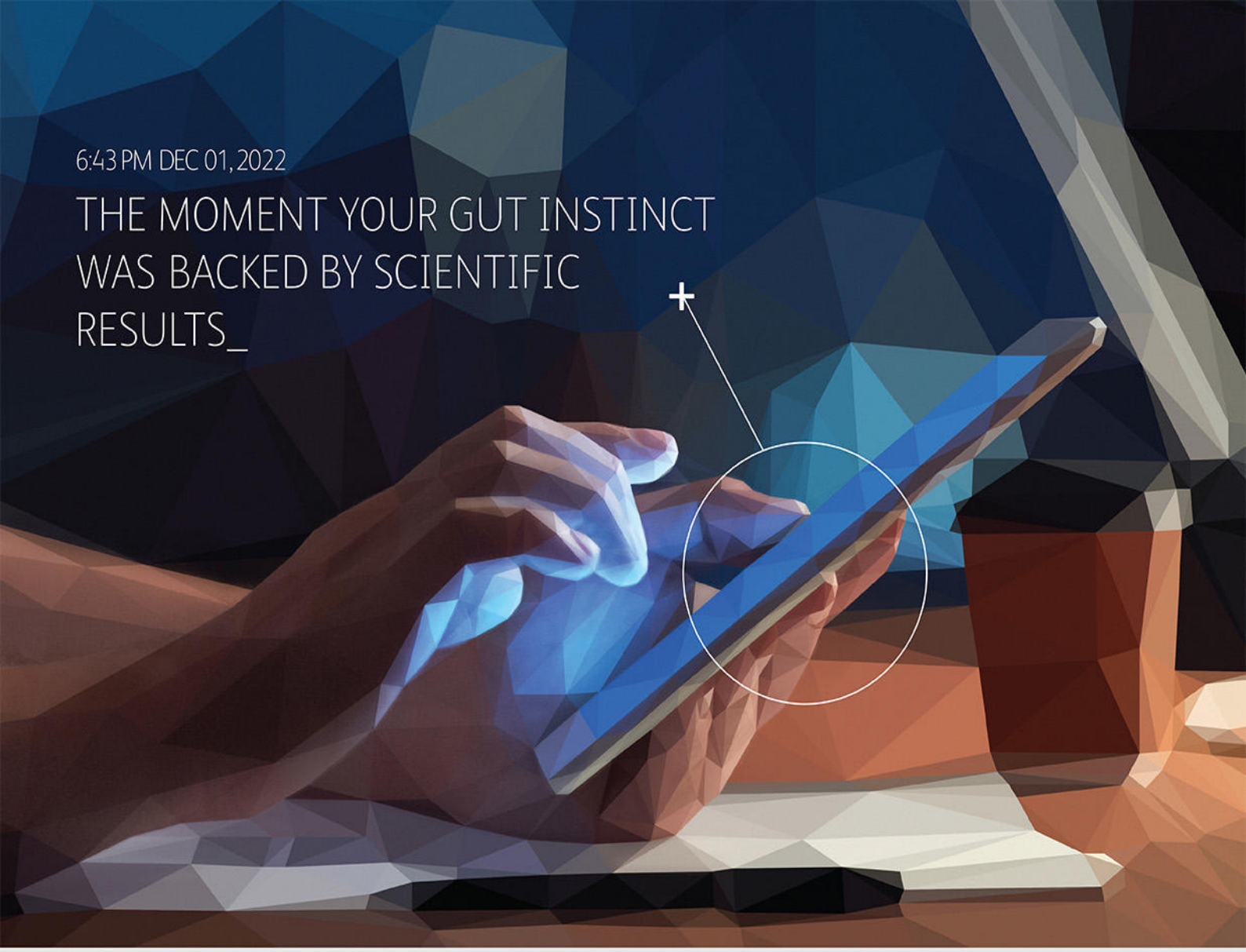
Multiple Myeloma						
N° subj/cases	46,118/ 272	82,723/ 536		170,760/ 586	119,663/ 485	
BMR residuals	1.06 (0.94; 1.19)	1.12 (1.06; 1.19)	0.013	1.02 (0.97; 1.07)	1.02 (0.99; 1.06)	0.522
Breast						
N° subj/cases	-	-		130,681/ 6,196	101,445/4,462	
BMR residuals	-	-		1.05 (1.03; 1.07)	1.02 (1.01; 1.03)	0.009
Endometrium						
N° subj/cases	-	-		130,681/ 553	101,445/ 779	
BMR residuals	-	-		1.06 (1.01; 1.11)	1.12 (1.09; 1.14)	0.402
Ovary						
N° subj/cases	-	-		130,681/ 527	101,445/ 457	
BMR residuals	-	-		1.03 (0.97; 1.09)	1.04 (1.00; 1.07)	0.170

Note. BMR residual: 1-standard deviation increase. Models were stratified by center and age and adjusted for education, physical activity, smoking, alcohol consumption, dietary intake (energy intake, meat intake, fish and shellfish intake and fibre intake), self-reported diabetes at recruitment, hormonal replacement (for women only) and BMI. Additional adjustment for menopause status, oral contraceptive, age at menarche and age at first full-term pregnancy for women-only cancer sites. **P*-value for heterogeneity explored by modelling interaction terms between BMR and BMI group. [a]Hepatocellular Carcinoma. Normal weight= BMI between 18.5 and 24.9 kg/m^2. Overweight= BMI 25 kg/m^2 or over. [¥]No sufficient cases.





Although the basal metabolic rate (BMR) –defined as the daily rate of energy metabolism required to preserve vital functions– has been associated with increased breast cancer risk, its relevance in other cancers remains unknown. Here, the authors examined associations with 13 cancers in over 500,000 individuals in Europe. Among normal-weight individuals, BMR was positively associated with cancers of the colon, pancreas, thyroid, esophageal adenocarcinoma, postmenopausal breast, and endometrium, pointing to BMR as a way to identify subgroups of the population who are at greater risk of these malignancies.



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