Master of public health

Master de Santé Publique

Joint association of body mass index and physical activity with cancer risk: Results from the prospective E3N cohort

Fareedah OREDOLA:

MPH 2019-2021, Master II.

Specialization: Biostatistics

Location of the practicum:
Inserm U1018, Centre for Research in Epidemiology and Population Health (CESP) ─ "Exposome, Heredity, Cancer, and Health" Team, Gustave Roussy, Paris, France

Professional advisor: Yahya Mahamat-Saleh, INSERM.

Academic advisor: Simon Combes, EHESP.

AKNOWLEDGEMENT

First of all, I am grateful to my parents, Bola and Lanre, who always make sure I get everything I want in life, even if they have to make personal sacrifices, but to them it’s not a sacrifice, it’s just love.

I want to thank Habubu, the best big brother a girl could ever ask for.

Sometimes in life we think we know what we want, and then life gives us something even better than what we want. I am grateful to God, to Whom my life belongs and Who never seizes to amaze me.

I especially want to thank my professional supervisor, Yahya Mahamat-Saleh, I can bet that in 2021, France, I got the best supervisor. He was ALWAYS available to answer my questions, to correct my mistakes and to help me grow. I could not have asked for a better supervisor.

I am grateful to the amazing friends I made in Paris (TMJASHLMAB).

Last but not the least, I would like to say a big thank you to Fafa, without whom all this would not have been possible, I am so proud of you Fafa, keep being the amazing person you are and keep soaring higher and higher. Love you.

ABSTRACT

Background: Overweight and obesity are associated with a higher risk of at least 12 different types of cancer. Sedentary behaviour and low physical activity are also associated with a greater risk of many cancers. Although, large body of evidence have explored the cancer risk associated with physical activity and obesity individually, very few studies have examined the joint effect of body mass index (BMI) and physical activity on cancer risk. This study aimed to investigate the joint effect of body mass index and physical activity on the risk of cancer in the E3N cohort.

Methods: E3N is a prospective cohort of 98,995 French women aged 40–65 years and followed up since 1990. Cancer cases were confirmed through pathology reports. Self-reported BMI was calculated by dividing weight by height at baseline. Baseline physical activity was assessed in metabolic equivalents of task. Cox model proportional hazards regression models was used to compute Hazard (HRs) and confidence intervals (95% CIs) adjusted for age and main known cancer risk factors.

Results: Between 1990-2014, a total of 16,548 cancer cases were ascertained among 92,097 women. Breast cancer was the most commonly diagnosed cancer, followed by colorectal, melanoma and lung cancer.

Compared with normal weight participants, overweight and obese participants had higher risks of overall cancer (HR=1.08, 95% CI=1.03-1.31 and HR=1.20, 95% CI=1.09-1.31, respectively). When considering cancer type, the strongest association was observed for endometrial cancer (HR=3.51, 95%CI=2.61-4.72, for obese versus normal, $P_{\text{-trend}}$=<0.0001), and colorectal cancer (HR=1.39, 95%CI=1.01-1.93, for obese versus normal, $P_{\text{-trend}}$ =0.08).

Regarding physical activity, participants with high levels of physical activity had a lower risk of overall cancer compared to those with low physical activity (HR=0.93, 95%CI=0.89-0.97, for quartile 4 versus quartile 1, P-trend=0.001). Specifically, high physical activity was associated with lower risks of breast cancer (HR=0.85, 95%CI=0.80-0.97, for quartile 4 versus quartile 1, P-trend=<0.0001). Our joint analyses revealed that reducing levels of physical activity were associated with higher risk of overall cancer among overweight and obese women. For example, compared with participants with normal weight and high physical activity, obese women with low physical activity had a higher risk of overall cancer (HR=1.29, 95% CI=1.11–1.51).

Conclusion: Our study suggests that overweight and obesity were associated with higher risk of overall cancer, whereas high physical activity was associated with lower risk of overall cancer. Our findings support the hypothesis that physical activity mitigates the excess risk of cancer associated with higher BMI among women.

This suggests that overweight or obese participants should be encouraged to increase their physical activity levels in order to reduce their risk to develop cancer. If confirmed, our findings may have important public health implications.

RÉSUMÉ

Contexte: Le surpoids et l'obésité sont associés à un risque accru de développer au moins 12 cancers différents. L'inactivité physique et les comportements sédentaires favorisent également la survenue de plusieurs cancers différents. Bien qu'un grand nombre d'études aient examiné l'effet de la charge pondérale et l'activité physique sur le risque de cancers, très peu d'études ont examiné l'effet joint sur le risque de cancers. L'objectif de cette étude est d'étudier l'effet joint de l'indice de masse corporelle (IMC) et de l'activité physique sur le risque de cancers dans la cohorte E3N.

Méthodes: E3N est une cohorte prospective incluant 98 995 femmes françaises nées en 1925-1950 et suivies depuis 1990. Les cas de cancers ont été confirmés par compte rendu pathologique. L'IMC à l'inclusion a été calculé en divisant le poids par la taille. L'activité physique à l'inclusion a été estimée en équivalent métabolique d'une tâche. Les analyses ont été réalisées à l'aide de modèles de Cox ajustés sur les principaux facteurs de risque connus de cancers.

Résultats: Entre 1990-2014, un total de 16 548 cas de cancers ont été déclarés parmi les 92097 femmes incluses dans l'analyse. Le cancer du sein était le plus fréquemment diagnostiqué, suivi du cancer colorectal, du mélanome ainsi que du cancer du poumon.

Comparé aux participantes ayant un IMC normal, celles en surpoids et obèses avaient un risque accru de tous cancers (Hazard Ratio (HR)=1,08, intervalle de confiance à 95% (IC)=1,03-1,31 et HR=1,20, IC=1,09-1,31, respectivement). Nos résultats par type de cancers suggèrent que l'association positive était plus forte pour le cancer de l'endomètre (HR=3,51, IC=2,61-4,72, pour obèses rapport à celles ayant un IMC normal, P-tendance=<0,0001) ainsi que pour le cancer colorectal (HR=1,39, IC=1,01-1,93, P-tendance=0,08).

En ce qui concerne l'activité physique, les participantes ayant un niveau élevé d'activité physique avaient un risque faible de tous cancers comparé à celles ayant un niveau faible d'activité physique (HR=0,93, IC=0,89-0,97, pour quartile 4 par rapport au quartile 1, P-tendance=0,001). Plus précisément, un niveau élevé d'activité physique était associé à un risque faible de cancer du sein (HR=0,85, IC=0,80-0,97, P-tendance=0,0001).

Nos résultats évaluant l'effet joint de l'obésité et de l'activité physique ont révélé que des faibles niveaux d'activité physique étaient associés à un risque accru de tous cancers chez les femmes en surpoids et obèses. A titre d'exemple, comparé aux participantes ayant un IMC normal et un

niveau élevé d'activité physique, celles obeses et ayant un niveau faible d'activité physique avait un risque accru de tous cancers (HR=1,29 ; IC=1,11-1,51).

Conclusion: Notre étude suggère que le surpoids et l'obésité étaient associés à un risque accru de tous cancers, alors qu'un niveau élevé d'activité physique élevée était associé à un risque faible de tous cancers. Les résultats de cette étude supportent l'hypothèse selon laquelle l'activité physique pourrait atténuer l'excès de risque de cancers associé au surpoids et l'obésité chez les femmes.

Nos résultats visent à encourager les femmes surpoids ou obèses à augmenter leur niveau d'activité physique afin de réduire leur risque de développer un cancer. Si ces résultats se confirment, ils peuvent jouer un rôle important en termes de prévention primaire de cancer.

TABLE OF CONTENT

LIST OF FIGURES AND TABLES

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVATIONS

AICR	American Institute for Cancer Research
ANOVA	Analysis of variance
BMI	Body mass index
CI	Confidence Interval
E3N	Etude Epidémiologique auprès de femmes de l'Education Nationale
GLOBOCAN	Global Cancer Incidence, Mortality and Prevalence
HR	Hazard ratio
IARC	International Agency for Research on Cancer
IC	Intervalle de confiance
IGFBP1-3	Insulin Like Growth Factor Binding Protein 1-3
IGFs	Insuline-like growth factors
IL 1-12	Interleukin 1-12
IMC	l'indice de masse corporelle
MET	Metabolic equivalent task
MGEN	Mutuelle Générale de l'Education Nationale
PA	Physical activity
Q1-14	Questionnaire 1-14
ROS	Reactive oxygen species
SHBG	sex hormone-binding globulin
TNF-a	Tumor necrosis factor- α
WCRF	World Cancer Research Fund
WHO	World Health Organization
X^2	Chi-squared test

1. INTRODUCTION

1.1. Cancer

Cancer is a group of diseases in which some of the body's cells grow uncontrollably and spread to other parts of the body through the blood and lymph systems. If the spread is not controlled, it can result in death. From a molecular level, cancer can be defined as series of successive mutations in genes that causes mutational changes to cell functions (Hassanpour & Dehghani, 2017). Irrespective of the inability to define cancer in simple terms, cancer is a major health problem globally and a leading cause of death in many high income countries (Micheli et al., 2002, Whiteman & Wilson, 2016).

According to GLOBOCAN, 19.3 million new cancer cases were diagnosed in 2020 (Sung et al., 2021) and these are expected to increase by 47% over the next two decades. There were over 10 million cancer deaths worldwide in 2020 (Sung et al., 2021). The most common cancer types diagnosed in women were breast (Kamangar et al., 2006), lung, colorectal, uterine and cervical cancers (Parkin et al., 2005) while the most common among men are cancers of the prostate, lung, colorectal, stomach, livers and bladder (Sung et al., 2021). Cancer incidence rates vary across countries with 2 to 3-fold higher overall incidence in developed countries versus less developed countries for both sexes, whereas mortality varied <2-fold for men and little for women (Sung et al., 2021). For both sexes combined, Asia contributes to about 44.9% to 49% of the total number of new cancer cases in the world (Kamangar et al., 2006, Sung et al., 2021), of which nearly half are found in China (**Figure 1**). Similarly, the cancer deaths in Asia constitute 58% of that in the world. Europe countries account for 22.8% of the total cancer cases and 19.6% of the cancer deaths, followed by the Americas 20.9% of incidence and 14.2% of mortality worldwide and lowest incidence (5.7%) and mortality (7.2%) were found in Africa (Sung et al., 2021).

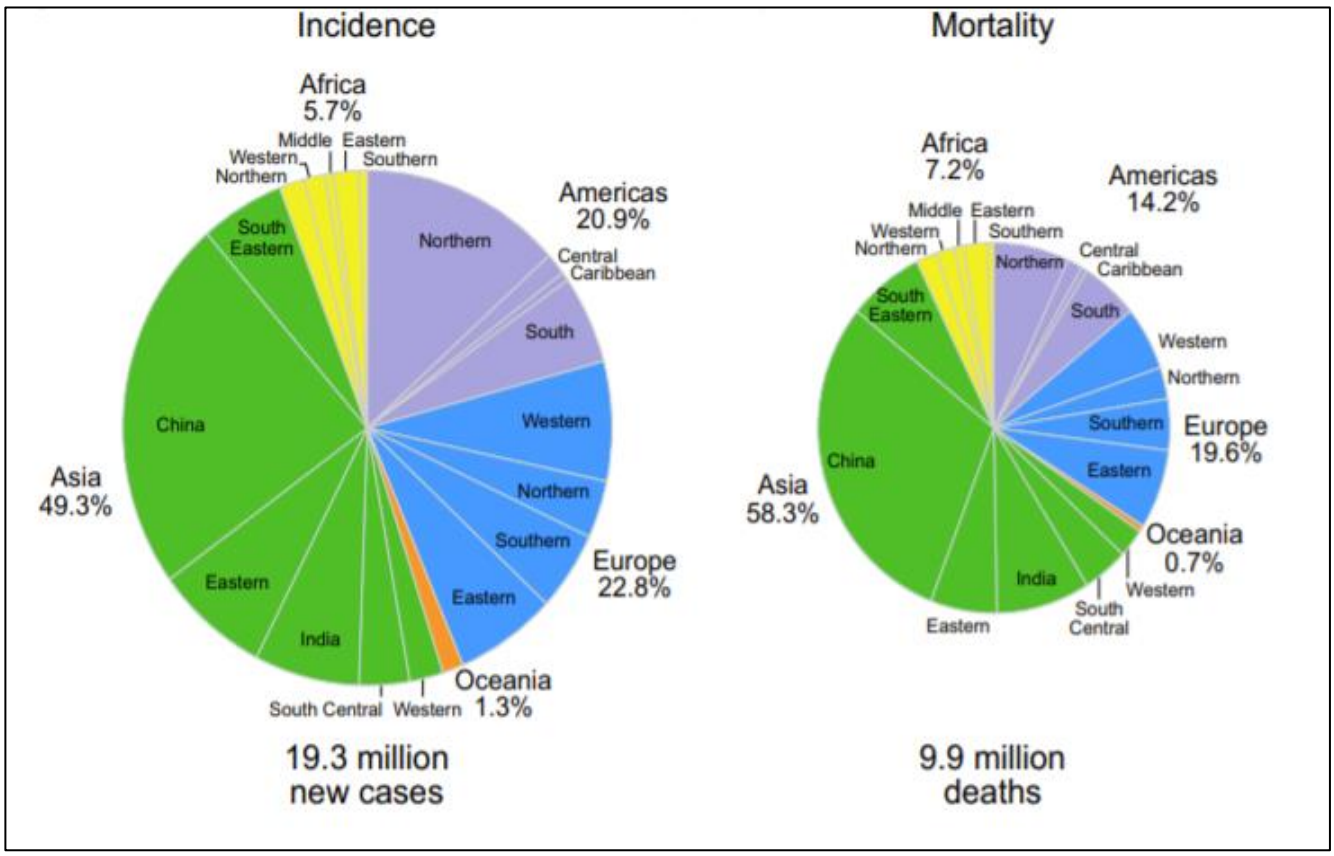

Figure 1: Distribution of cases and deaths by world Area in 2020 for both sexes. Source: GLOBOCAN 2020 (Sung et al., 2021).

In France metropolitan, cancer is the leading cause of death. In 2017, it was estimated that there were 400,000 new cancer cases (214,000 men and 185,500 women) and 150,000 deaths (84,000 men and 66,000 women) (Colonna et al., 2018). In men, lung cancer is the main cause of death, followed by colorectal and prostate cancers. In women, it is breast cancer followed by colorectal and lung cancers (Cowppli-Bony et al., 2019).

Cancer prevalence increases as a population ages, currently, the burden of cancer prevalence is being managed by screening and timely detection; this is highly contributed in the fight against cancer but unlikely to make a big impact, therefore, it is important to consider the role of primary prevention (Wiseman, 2008, Bellocco et al., 2016). Cancer is a multifactorial disease arising from the interactions of a complex etiology involving genetic, environmental and lifestyle factors (Anand et al., 2008), thus there is great need and opportunity for cancer prevention through lifestyle change. It has been suggested that about 40% of cancers are potentially preventable (Friedenreich et al., 2021). Modifiable risk factors such as diet, smoking, physical

activity and BMI, highly contribute to cancer development (Arem & Loftfield, 2018). Overweight/obesity, physical inactivity and sedentary behavior are the main factors associated with an increased risk of cancer (IARC, 2020), whereas, tobacco is one of the most important risk factor (WHO, 2021).

1.2. Literature on BMI, physical activity and cancer risk

1.2.1. BMI

Obesity and overweight are currently major public health problems around the world due to their rapidly growing prevalence and their deleterious impact on many chronic diseases (Lancet, 2016). Globally, as of 2016, around 2 billion adults are overweight (about 39% of the world population), of which more than 600 million are obese (about 14% of the world population) (WHO, 2020). Obesity leads to a number of new cancer cases each year, with approximately 4% of new cancer cases attributable to obesity or overweight (Arnold et al., 2016). Overweight and obese have been reported to increase the risk of at least 12 different types of cancer (Secretan et al., 2016) and large-scale epidemiological studies have indeed consistently presented the association between body fatness and the risk of several cancer types (Katzke et al., 2015). According to International Agency for Research on Cancer (IARC) and World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR), there is sufficient evidence to declare overweight and obesity as a cause of endometrial, esophageal, kidney, colon and breast cancer (Wiseman, 2008, Whiteman & Wilson, 2016, Wilson et al., 2019). However, evidence of other cancer type was limited.

1.2.2. Physical activity

Physical activity is known to reduce risks of heart disease and all-cause mortality, as well as risks of cancer (Rezende et al., 2018, Mctiernan et al., 2019). Low physical activity increases the risk of not only three different cancers, particularly colon, breast, and endometrial cancers but also esophageal cancer, liver cancer, stomach cancer, kidney cancer, and myeloid leukemia (Moore et al., 2016). It is challenging to identify the distinct effect of physical activity on cancer risk, mainly because of the difficulties in assessing the physical activity pattern of an individual (Katzke et al., 2015). Nonetheless, the health benefits of physical activity are well established (Garcia, et al., 2018), the 2018 WCRF/AICR report concluded that there is strong evidence that

higher levels of physical activity are linked to lower risk of some types of cancer, particularly that of breast, colon and endometria cancer (Cannon, 2008). Less is known, however, about whether physical activity reduces risk of other cancers, which, together, constitute 61% of cancers worldwide (Ferlay et al., 2015).

1.2.3. Joint effect of BMI and physical activity

Globally, there is strong evidence that overweight/obesity, physical inactivity and sedentary behavior independently influence the risk of numerous types of cancers. Despite the large body of evidence examining the cancer risk associated with physical activity and excess body fatness, typically measured using BMI, very few studies have thoroughly examined the joint effect of BMI and physical activity (Conroy et al., 2009, Bellocco et al., 2016). Some studies have explored the modifying effect of BMI on physical activity and vice versa on the risk of cancer. Thune and colleagues reported 72% reduction in breast cancer in lean women who exercised regularly (Thune et al., 1997). McTiernan and colleagues reported a strong and significant reduction in breast cancer for women having normal BMI with increasing level of physical activity (McTiernan et al., 2003). In a study conducted by Dirx and colleagues, physical activity was found to be inversely associated with breast cancer risk in low BMI category (Dirx et al., 2001). Several others studies have reported similar results (Yang et al., 1998, Colditz et al., 2003, Peters et al., 2010, Ratnasinghe et al., 2010, Holmes & Willett, 2011). However, some studies reported no modifying effect of BMI on physical activity in relation to breast cancer risk (Suzuki et al., 2008). Unfortunately, these studies are mainly focus on breast cancer risk and very few studies have explored other cancer type. Therefore, it is crucial to investigate joint associations with other cancer types.

1.3. Research aim and objective

Within this context, the current study aims to investigate the association between BMI as well as physical activity and the risk of cancers in the E3N (Etude Epidémiologique auprès de femmes de l'Education Nationale) cohort, a prospective cohort of ~ 100 000 French women living in France, aged 40 to 65 years old at baseline, and insured by the Mutuelle Générale de l'Education Nationale (MGEN), a French insurance scheme for teachers and co-workers.

The a priori hypothesis is that high BMI increases the risk of all cancer and 10 specific cancers and that being more physically active reduces the risk of all cancer and 10 specific cancer types. We also hypothesize that women with higher BMI who report low level of physical activity are at higher risk of all cancers and those with normal BMI and highly active are at lower risk of cancer.

Our specific objective was the following:

Aim 1: To investigate the relations between BMI and risk of overall cancer.

Aim 2: To explore the relations between physical activity and risk of overall cancer.

Aim 3: To examine the joint effect of BMI and physical activity and risk of overall cancer.

In addition, these associations was analyzed by specific cancer types

2. MATERIAL AND METHODS

2.1. Data and study design

This study utilizes data from the E3N cohort, a French prospective cohort set up in metropolitan France in 1990 and which is still ongoing. E3N consists of ~100,000 women born between 1925 and 1950, aged 40 to 65 years old at baseline, and insured by the MGEN, a French insurance scheme for teachers, co-workers and their families.

E3N was initiated to investigate the risk factors associated with major non-communicable diseases in women, particularly cancer. Women were enrolled in 1990 after returning a baseline self-administered questionnaire on their lifestyle and medical history along with informed consent. Follow up questionnaires were sent every 2–3 years thereafter (**Figure 2**) and addressed medical events such as cancer, which were confirmed through pathology reports. Response rates were for the most part approximately 80%–85% at each questionnaire throughout follow-up. The E3N cohort received ethical approval from the French National Commission for Data Protection and Privacy (Commission Nationale de Informatique et des Libertés).

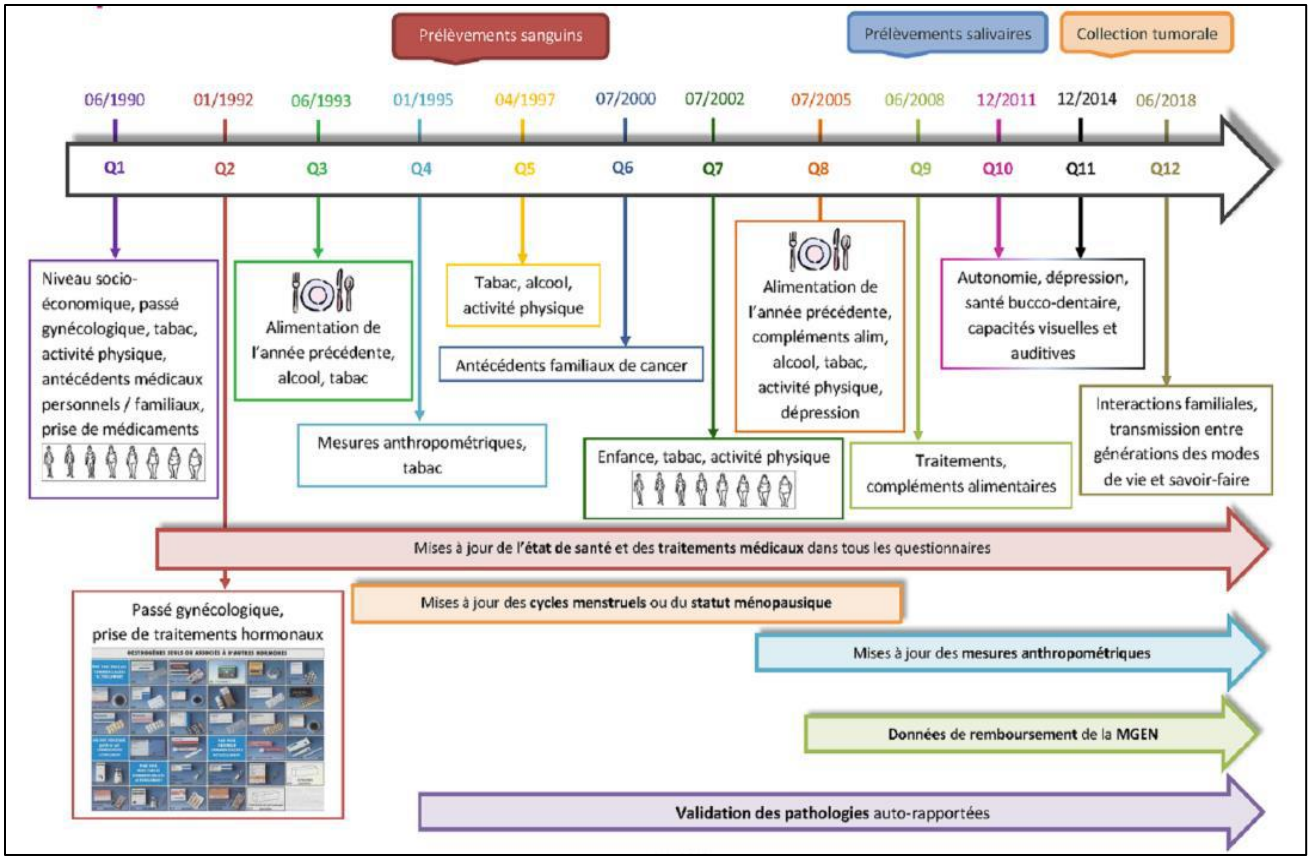

Figure 2: Chronology of the E3N questionnaires and the different data collected.

2.2. Study population

Follow-up started at the date of return of the 1990 questionnaire. Women contributed person-time from the return date of the first questionnaire on BMI and physical activity until the date of cancer diagnosis, date of last completed questionnaire, or date of end of follow-up (June, 2014), whichever occurred first. Of the 98,995 participants from the E3N cohort study, we first excluded participants with no follow up and those with prevalent cancer at baseline (n=6,898), leaving a first dataset of 92,097 participants. We further excluded participants who did not answer the baseline questionnaire requesting BMI (n=2,079), leaving a total of 90,018 participants for the analysis of BMI. Based on the first dataset, we then excluded participants who did not have information on baseline physical activity (n=1,248), leaving a total of 90,849 participants for the analysis of physical activity. For the analysis of the joint effect, we excluded participants who did not have information on both BMI and physical activity, leaving total 89,140 participants for this analysis (**Figure 3**). Details of the cohort have been previously reported (Clavel-Chapelon, 2015).

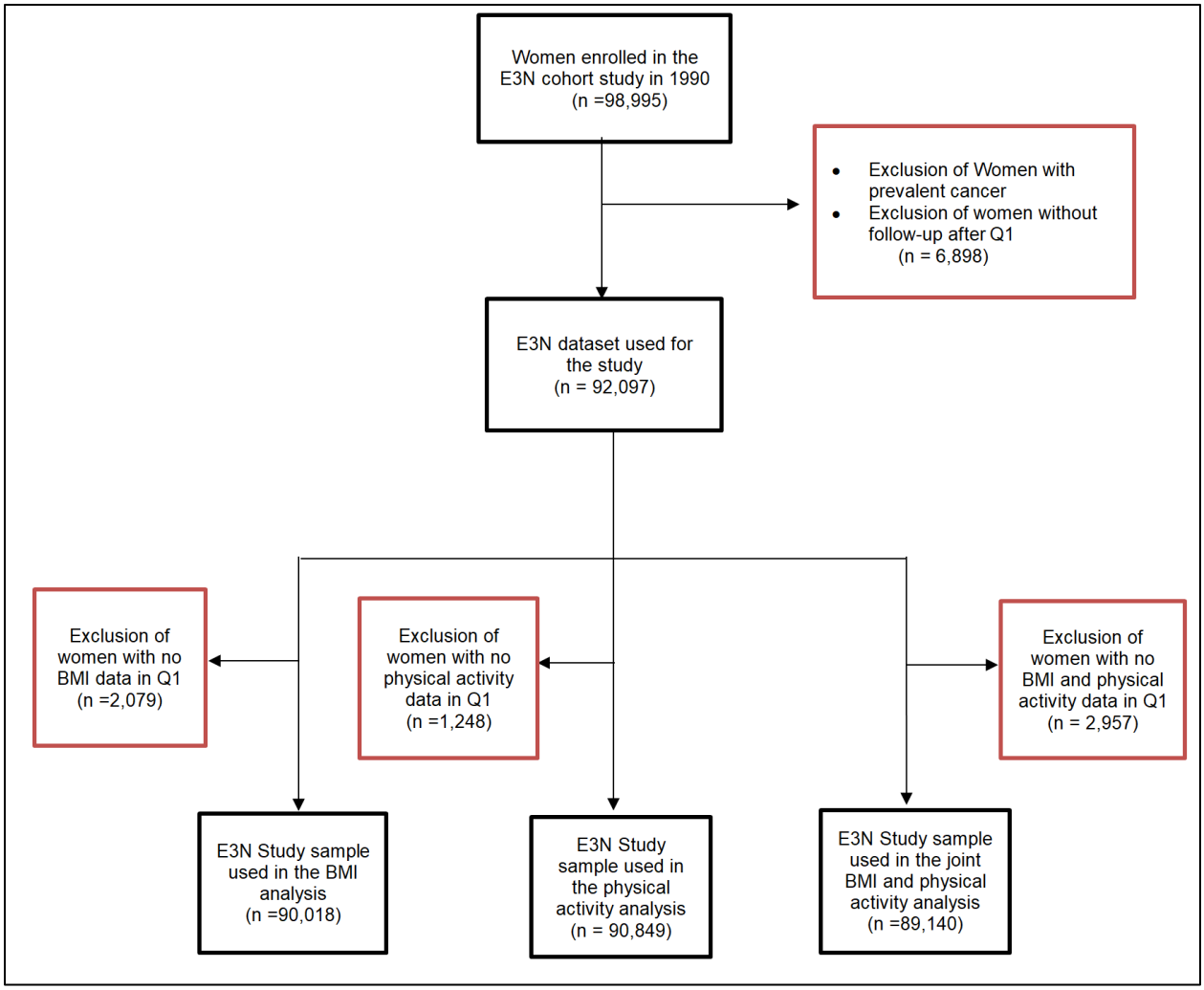

Figure 3: Flow chart of the study population, E3N cohort, 1990–2014.

2.3. Variables

2.3.1. Identification of incident cancers

Cases were defined as women diagnosed with a first cancer (either in situ or invasive, excluding metastases) located in all organs during the follow-up. Each questionnaire included a health section in which women were asked to report whether they were diagnosed with cancer(s) since the last questionnaire and to provide the date of diagnosis, as well as details of their attending physician(s) and any histopathology assessment of the cancer(s) in their possession (Dartois et al., 2014). The self-reported cancer cases were then verified and coded and the histopathology assessments were collected from the physicians. The histopathology reports contained valuable

information, such as the date of diagnosis, the grading and the location of the tumor. Cancer deaths were also taken into account in order to identify cancers that were not reported. Deaths in the cohort were ascertained from reports by family members and by searching the insurance company file that contains information on vital status. Information on cause of death was obtained from the French National Service on Causes of Deaths. Information on non-respondents was obtained from the MGEN file on reimbursement of hospital fees.

2.3.2. Assessment of BMI and physical activity

In the cohort, habitual physical activity was assessed at baseline (1990), in the 1993, 1997, 2002, 2005 and 2014 questionnaires. Assessment of physical activity was based on six similar questions for Q1 which included: distance walked in meters per week, participation in intense physical activity, participation in moderate physical activity, heavy housework, light housework and number of flight of stair climbed. Physical activity was assigned a metabolic equivalent task (MET) score as followed: 0.00075 for walking, 7.5 and 5 for intense and moderate activity respectively, and 3 for heavy and light housework, respectively. MET-h/week was calculated as the reported or averaged hours per week engaged in the activity multiplied by the assigned MET score. A total MET-h/week was estimated by summing up the MET of all the activities engaged in for each participant. For this present report, we did not consider physical activity collected at the 1993, 1997, 2002 and 2005 questionnaires. These questionnaires will be considered subsequently, however the results are not included in this report.

The weight at adulthood was self-reported in each of the seven consecutive questionnaires used in this study. Height at adulthood was self-reported in the first (sent out in 1990), fourth (sent out in 1995), sixth (sent out in 2000), seventh (sent out in 2002) and eighth (sent out in 2008) questionnaires and a standardized height was calculated as the mean height of all the available reported heights. BMI was then computed at each questionnaire as weight/ height in kg/m2, using the closest available weight and the standardized height for all questionnaires. Here again, we did not consider BMI collected at the different questionnaire. However, baseline BMI was used in the present study.

2.3.3. Assessment of co-variables

The following section outlines the details of the co-variables used in the present report:

a) Personal characteristics: age at the recruitment, generation (≤1930, 1931-1935, 1936-1940, 1941-1945, ≥1946 years of birth), education (<12 years, 12-14 years, >14 years at school), marital status (single, married/live-in-partner, widowed, divorced/separated).
All these information were collected at baseline.

b) **Health behavior:** smoking status (never smoker, former smoker, and smoker) was collected at different questionnaire and information about diet at the 1993 questionnaire.

c) **Reproductive characteristics** included age of first menstruation, age of menopause, regularity of menstrual cycles (<25 days, 25-32 days, >32 days, irregular, do not know), age of first pregnancy (≤22years, 23-25 years, >25 years), use of contraceptive pills before first pregnancy (yes/no), use of contraceptive pills (yes/no), use of hormonal pills (yes/no), menopause status (yes/no) and breastfeeding (yes/no).

d) **Individual predisposing characteristics:** family history of cancer (yes/no); having diabetes mellitus (yes/no).

2.4. Statistical analyses

Statistical analyses were performed using SAS statistical software (SAS Institute Inc., Cary, North Carolina, USA).

2.4.1. Descriptive statistics

Distribution of baseline characteristics according to BMI and total physical activity categories were described using X^2 tests for categorical variables, and ANOVA for continuous variables. BMI categories were created using the WHO classification of under-weight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2) overweight (25.0-29.9 kg/m^2), and obese (≥ 30kg/m^2). Physical activity was categorized using quartiles, quartile 1 (0.0–26.50 MET-h/week), quartile 2 (26.6–38.4 MET-h/week), quartile 3 (38.5–54.9 MET-h/week) and quartile 4 (55.1–223.8 MET-h/week).

2.4.2. Cox regression analysis model

Cox proportional hazard models with age as the time scale were used to estimate the Hazard Ratio (HR) and 95% confidence intervals (95% CI) of the association between physical activity and BMI and risk of total cancer. The model can be simply represented with the equation below.

$$h(t|x) = h_0(t)e^{\beta_1 x_1 + \ldots + \beta_p x_p},$$

Where $h(t|x)$ stands for the hazard at time t for one subject with a set of explanatory variable $x_1,\ldots x_p$, the baseline hazard function is $h_0(t)$ and the model parameters are $\beta_1,\ldots, \beta_p$.

Analyses were performed separately for BMI and physical activity and then jointly, for all cancer and by cancer types.

We performed three models. The first model was adjusted for age and stratified by birth cohort (1925–1930, 1930–1935, 1935–1940, 1940–1945, 1945–1950)) to consider a possible cohort effect (model 1), the second model was additionally adjusted for potential confounders, such as education level, smoking status, marital status, diabetes, family history of cancer, healthy dietary pattern, as previously created, age at menarche, use of oral contraceptives, age at first birth and age at menopause. Regarding analysis for BMI, the second model was additionally adjusted for physical activity (Model 3), whereas, this second model was additionally adjusted for BMI in the analysis of physical activity (Model 3).

Values were missing in <5% of observations for all adjustment variables and were imputed to the median or modal categories in our population. All statistical tests were 2-sided, and significance was set at the 0.05 level.

3. RESULTS

3.1. Baseline characteristics of study population according to BMI and physical activity levels

Over 1990-2014, a total of 16,548 cancer cases were diagnosed among 90,180 women (median years of follow-up=24 years). Breast cancer was the most commonly diagnosed cancer, followed by colorectal cancer, melanoma and lung cancer (**figure 4**).

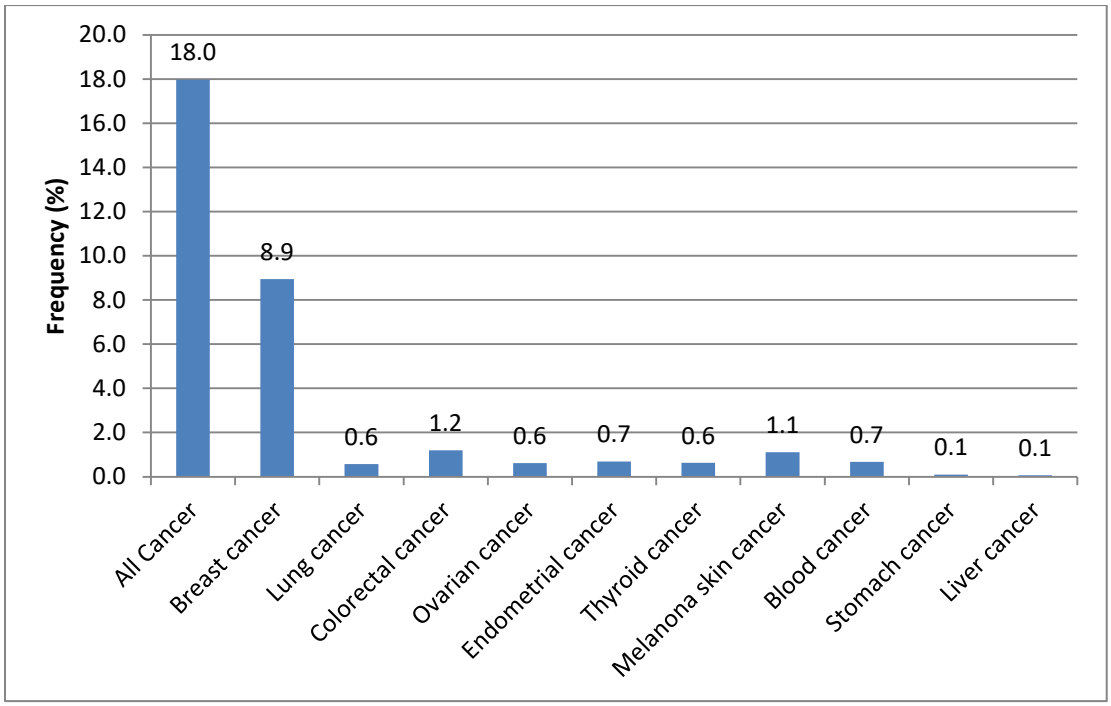

Figure 4: Cancer frequency in E3N study population, n=92,097, E3N cohort, 1990-2014.

Compared with obese women, participants with normal BMI were slightly younger and more likely to be educated, physically active, to be current smokers, to be married and more likely to have a their first full term pregnancy at later age, ever used of oral contraceptive, and less likely to have family history of cancer, hypertension and diabetes. We observed the opposite findings when participants with normal BMI were compared to underweight participants (**Table 1**).

Participants with high physical activity were slightly older and less liked to be educated but they were more likely to non-smokers, married and to have a heathy adherence to diet, to have breastfed, never used oral contraceptive compared to those with low physical activity (**Appendix 2**).

Table 1: Baseline characteristics of study participants according to Body Mass Index levels, n=90,018, E3N cohort, 1990–2014

	BMI CATEGORY			
	Under weight <18.5	Normal weight 18.5-25	Over weight 25-30	Obese >=30
CHARACTERISTICS	(n=3,835)	(n=70,202)	(n=13,187)	(n=2,794)
Age at baseline, mean(SD)	47.44 (6.31)	48.86 (6.48)	51.39 (6.87)	51.18 (6.83)
Year of birth (%)				
≤1930	6.81	8.45	15.80	15.14
1931-1935	9.00	12.35	18.68	18.54
1936- 1940	14.32	19.90	22.36	21.83
1941-1945	24.93	25.52	22.07	23.01
≥1946	44.95	33.79	21.09	21.47
Educational level (%)				
<12 years	11.47	14.54	23.29	28.81
12 – 14 years	46.41	49.66	50.88	48.57
> 14 years	42.11	35.80	25.84	22.62
Smoking status (%)				
Non smoker	51.47	53.95	56.60	55.05
Ex- smoker	28.84	30.88	30.91	31.93
Current smoker	19.69	15.17	12.49	13.03
Marital status (%)				
Single	21.38	17.15	17.74	22.41
Married	75.12	79.56	78.01	72.58
Missing	3.49	3.29	4.25	5.01
Dietary score (%)				
Quartile 1	20.91	18.33	16.41	15.10
Quartile 2	17.50	15.74	14.17	11.95
Quartile 3	21.77	22.93	20.85	19.90
Quartile 4	18.12	21.63	21.96	20.72
Missing	21.69	21.37	26.62	32.32
Physical activity category (%)				
Quartile 1	25.55	23.74	26.18	32.57
Quartile 2	25.68	25.20	23.93	22.19
Quartile 3	23.86	25.02	23.92	20.11
Quartile 4	23.96	25.09	24.90	23.91
Missing	0.94	0.95	1.06	1.22
Family history of cancer (%)				
No	20.81	20.63	20.43	19.01
Yes	79.19	79.37	79.57	80.99
Hypertension (%)				
No	87.30	85.74	83.67	85.47
Yes	12.70	14.26	16.33	14.53
Diabetes (%)				
No	99.06	97.67	91.13	75.38
Yes	0.94	2.33	8.87	24.62

Table 1. Continued	Under weight	Normal weight	Over weight	Obese
CHARACTERISTICS	(n=3,835)	(n=70,202)	(n=13,187)	(n=2,794)
Menopause status (%)				
Pre-menopausal	3.44	2.90	3.15	3.47
Menopausal type unknown	5.97	4.95	5.15	6.23
Menopausal, naturally	83.65	84.07	80.06	76.45
Menopausal artificially	6.91	8.06	11.62	13.85
Never mensturated	0.03	0.02	0.02	NA
Age at menarche (%)				
<13 years	35.18	43.88	52.83	58.95
13 -14 years	49.05	45.49	38.96	35.11
>14years	15.78	10.63	8.21	5.94
Age of first birth (%)				
<23 years	37.34	39.02	41.40	46.10
23 - 25 years	27.74	30.48	29.51	26.84
>25 years	34.92	30.49	29.09	27.06
Breastfeed (%)				
No	33.25	30.58	30.43	30.67
Yes	66.75	69.42	69.57	69.33
Ever use of menopausal hormone therapy (%)				
No	73.66	70.09	68.48	73.34
Yes	15.62	19.63	19.43	12.74
Missing	10.72	10.28	12.09	13.92
Ever use of oral contraceptives (%)				
No	40.81	41.60	55.17	60.31
Yes	59.19	58.40	44.83	39.69

3.2. Association between BMI and cancer risk

The results for the association between BMI and cancer risk are presented in **figure 5**.

We found that higher BMI value were significantly associated with a higher risk of overall cancer (P_{-trend}=<0.0001) in fully adjusted model. Compared with normal BMI participants, obese participants had 20% higher risk of overall cancer (HR=1.20, 95%CI=1.09-1.31); overweight participants had 8% increased risk of cancer (HR=1.08, 95%CI=1.03-1.13). When considering cancer type, obese women had 39% increased risk of colorectal cancer compared to normal weight women (HR=1.39, 95%CI=1.01-1.93). High values of BMI were associated with higher risk of endometrial cancer (HR=3.51, 95%CI=2.61-4.72, for obese versus normal BMI. P_{-trend} <0.0001 and HR=1.52, 95%CI=1.24-1.86, for overweight versus normal BMI, P_{-trend} =<0.0001). In addition, while, compared with normal BMI women, overweight participants had a 32% increased risk of thyroid cancer, under-weight was associated with low risk of thyroids cancer

(HR=0.55, 95%CI=0.31-0.95), although thyroids cancer risk was not significantly different in those with obesity compared to those with normal BMI (HR=1.47, 95%CI=0.93-2.30). However, we found no association between BMI and others cancer risk.

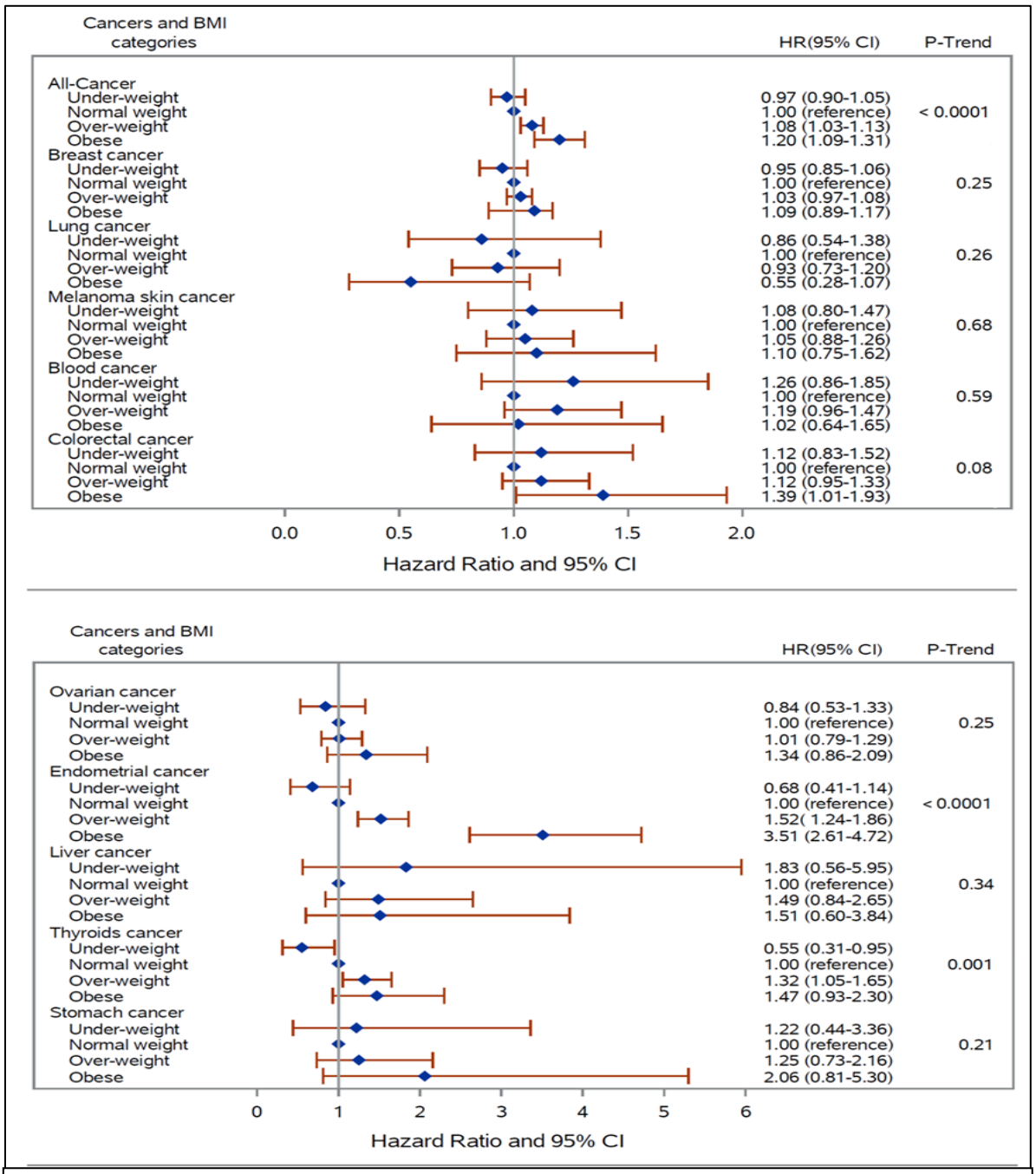

Figure 5: Forest plot of hazard ratios of association of BMI with all cancer and selected cancers with 95%CI, n=90,018, E3N cohort, 1990–2014.

The forest plot presents the results of the fully adjusted model of the association of BMI with cancer. Analyses were adjusted for education level, smoking status, use of oral contraceptive, use of menopausal hormonal therapy, family history of cancer, marital status, age of first full term pregnancy, age of menarche, menopausal status, breastfeeding, diabetes, dietary score and physical activity.

3.3. Association between physical activity and cancer risk

The results for the association between physical activity and cancer risk are presented in **figure 6**.

In the model adjusted on known risk factors for cancer, there was an inverse linear association between physical activity and risk of overall cancer ($P_{-trend} < 0.05$). Specifically, participants with high physical activity had 7% reduction in risk of overall cancer (HR=0.93, 95%CI=0.89-0.97, for quartile 4 versus quartile 1, $P_{-trend}=0.0012$). When we investigated analyses by cancer type, we found that high physical activity was associated with breast cancer risk (HR=0.85, 95%CI=0.80-0.90, for quartile 4 versus quartile 1, $P_{-trend}=<0.0001$). While there was a reduction in risk of blood cancer[1] with increasing level of physical activity, the HR was not statistically significant (HR=0.84, 95%CI=0.67-1.05, for quartile 4 versus quartile 1, $P_{-trend}=0.0721$). There was no significant association between physical activity and the risk of 8 other specific cancers.

[1] Blood cancer refers to lymphoma, a type of cancer that develops when lymphocytes grow out of control

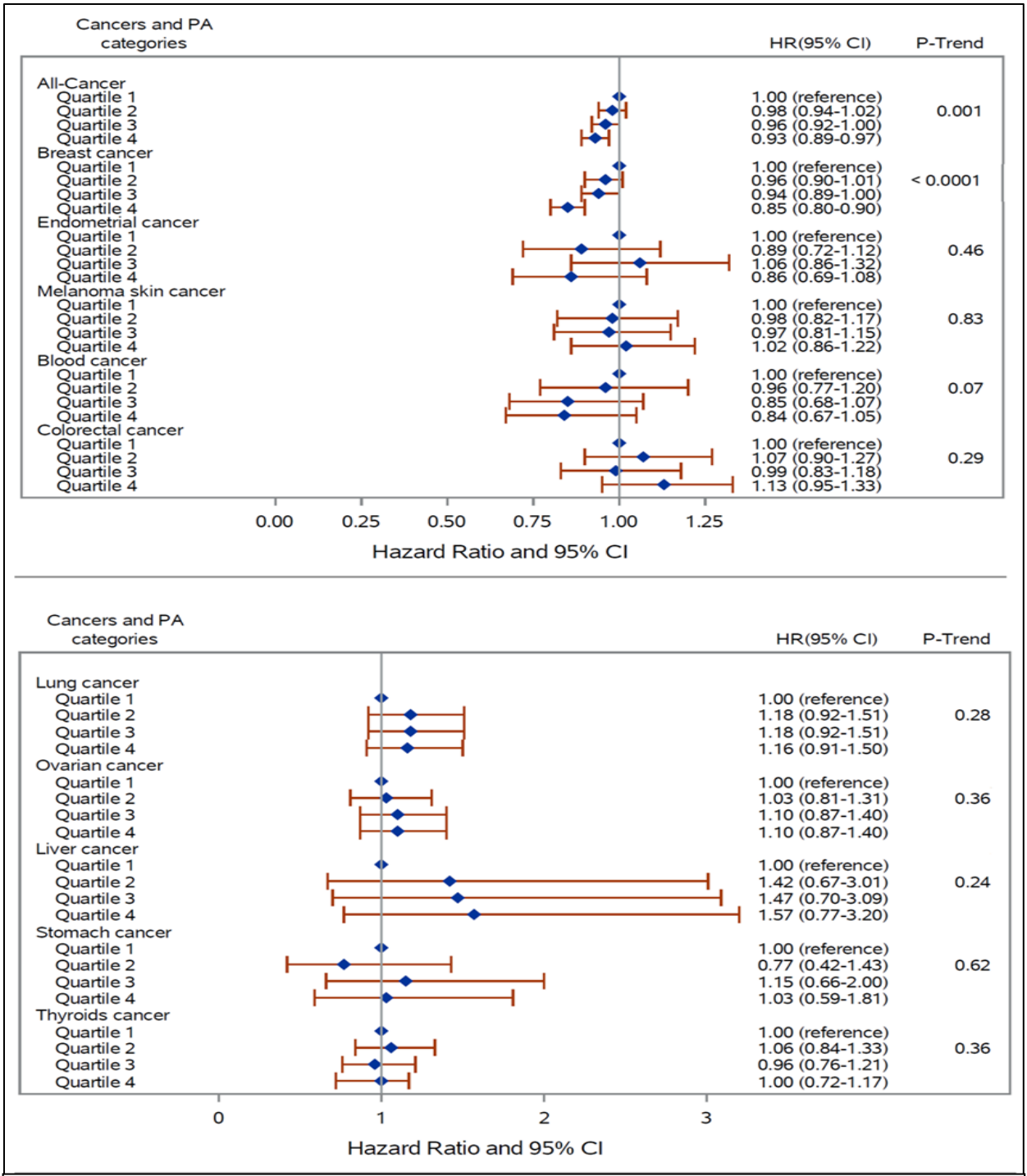

Figure 6: Forest plot of hazard ratios with 95%CI of association of physical activity with all cancer and selected cancers, n= 90,849, E3N cohort, 1990–2014.

The forest plot presents the results of the fully adjusted model of the association of physical activity with cancer outcomes. Analyses were adjusted for education level, smoking status, use of oral contraceptive, use of menopausal hormonal therapy, family history of cancer, marital status, age of first full term pregnancy, age of menarche, menopausal status, breastfeeding, diabetes, dietary score and BMI.

3.4. Joint effect of BMI and Physical Activity on Cancer risk

The results for the joint association of BMI and physical activity and overall cancer risk are presented in the **Table 2 and Figure 7**).

When considering the joint associations, we found that higher BMI was associated with a higher risk of overall cancer with evidence of a difference in risk with higher levels of physical activity. The HR of overall cancer was 7% higher in normal BMI women with low physical activity than in normal BMI high active women (HR=1.07, 95% CI=1.01-1.12). Compared with normal BMI high active women, overweight and obese women also had increased risk of cancer with reduction of physical activity. Physical activity therefore appeared to reduce the effect of BMI on cancer risk, and this was more apparent for overweight than for obese women. The HR of cancer was 12% higher in overweight women with moderate physical activity (HR=1.12, 95% CI=1.02-1.22) and 16% higher in overweight women with low physical activity (HR=1.16, 95% CI=1.07-1.26) than in normal BMI high active women, although there was no difference in risk when comparing healthy BMI high active women to overweight high active women (HR=1.06, 95% CI=0.97-1.16).

The HR of cancer was 25% higher in obese high active women (HR=1.25, 95% CI=1.05-1.50) and 29% higher in obese women with low physical activity (HR=1.29, 95% CI=1.11-1.51) than in healthy BMI high active women. In order word, while physical activity reduced the effect of overweight on overall cancer risk, this later slightly reduced but did not delete the effect of obesity on cancer risk.

Table 2: Hazard ratios and 95%CI of the joint effect of BMI and physical activity on the incidence of all cancer, n=89,140, E3N cohort, 1990–2014 [a]

BMI	Physical activity			
	Quartile 4	Quartile 3	Quartile 2	Quartile 1
Model 1[b]				
Under weight	0.84 (0.70-1.00)	1.07 (0.92-1.26)	1.05 (0.90-1.23)	1.14 (0.97-1.32)
Normal weight	1.00 (reference)	1.03 (0.98-1.08)	1.06 (1.01 1.11)	1.08 (1.03-1.14)
Over weight	1.03 (0.94-1.13)	1.09 (1.00-1.19)	1.13 (1.04-1.23)	1.15 (1.06-1.25)
Obese	1.16 (0.97-1.38)	1.07 (0.87-1.30)	1.17 (0.97-1.41)	1.22 (1.05-1.42)
Model 2[c]				
Under weight	0.82 (0.69-0.98)	1.05 (0.90-1.23)	1.02 (0.87-1.20)	1.10 (0.95-1.29)
Normal weight	1.00 (reference)	1.02 (0.97-1.08)	1.05 (1.00-1.10)	1.07 (1.01-1.12)
Over weight	1.06 (0.97-1.16)	1.12 (1.02-1.22)	1.14 (1.05-1.25)	1.16 (1.07-1.26)
Obese	1.25 (1.05-1.50)	1.15 (0.94-1.41)	1.25 (1.03-1.51)	1.29 (1.11-1.51)

[a] Values were estimated with the use of Cox proportional hazards models

[b] For age (timescale) and stratified by birth cohort (1925–1930, 1930–1935, 1935–1940, 1940–1945, 1945–1950).

[c] Additionally adjusted for education level, smoking status, use of oral contraceptive, use of menopausal hormonal therapy, family history of cancer, marital status, age of first full term pregnancy, age of menarche, menopausal status, breastfeeding, diabetes and dietary score

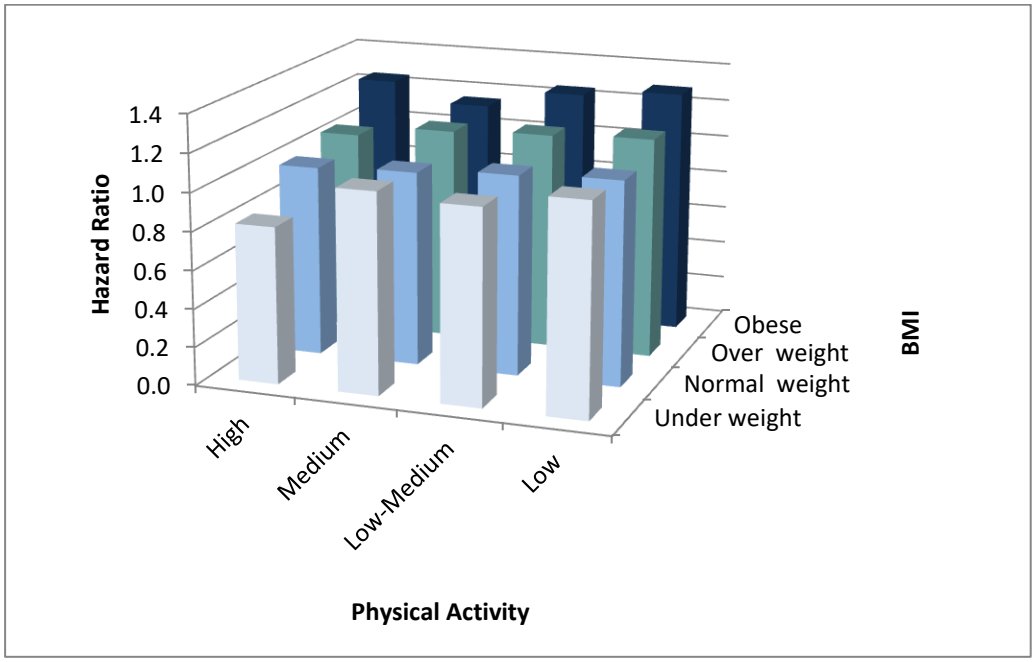

Figure 7: Joint association of BMI and PA on the risk of all cancer (adjusted model)

4. DISCUSSION

The results from this large prospective cohort of French women suggested that women with high BMI had a greater risk of overall cancer, whereas women with high level of physical activity had a lower risk of overall cancer. Specifically, we found that obesity was strongly associated with endometrial and colorectal cancer, while high level of physical activity was inversely and linearly associated with only breast cancer. When considering the joint effect of these factors, high level physical activity did not appear to mitigate the excessive risk of obesity on overall cancer; however, physical activity appeared to reduce the effect of overweight on cancer risk.

Several studies have investigated the individual associations between BMI and physical activity and cancer risk. Higher BMI not only increases cancer risk but can also increases cancer mortality (Arem et al., 2013). Results from a pooled prospective cohort by Moore and colleagues showed that physical activity is associated with lower risk of 13 out of 26 cancers (Moore et al., 2016). This pooled prospective cohort, the largest cohort to date including 1.44 million participants, revealed that physical activity was associated with more cancer risks than previous literature states (Arem & Loftfield, 2018). Higher levels of physical have been also reported to be associated with lower risk of overall cancer, according several meta-analyses (Mctiernan et al., 2019). Consistency, our study suggested that BMI and physical activity were individually associated with cancer risk. We found that BMI was particularly associated with endometrial and colorectal cancer, and physical activity was associated with breast cancer.

Previous studies have explored potential heterogeneity in the physical activity association by BMI, most of which have found similarly inverse associations in women with a BMI<25 compared to women with a BMI≥25 kg/m^2 (Friedenreich et al., 2021). The joint effect of BMI and physical activity was indeed recently studied by Maliniak and colleagues who found that leisure-time physical activity mitigates the excess risk associated with higher BMI for risk of breast, endometrial, or colon cancer among postmenopausal women (Maliniak et al., 2020). In our study, although, high level of physical activity did not appear to mitigate the excessive risk of obesity on overall cancer; we found that physical activity reduced the effect of overweight on cancer risk, which support results of studies done by (Maliniak et al., 2020). Since 30-40% of cancers can be prevented by lifestyle modification (Friedenreich et al., 2021), these finding may have may have important implication in the primary prevention of cancer in women in France but also worldwide, where the prevalence of cancer between 2010 and 2017 has increased in women (Cowppli-Bony et al., 2019).

There are several hypotheses on the biological mechanism in which BMI and physical activity influence cancer risk, some of which have been proved through experimental and observational research (Friedenreich et al., 2021). Although, the role of obesity in the cause and subsequent development of cancer cannot be fully explained, there are several pathways linking obesity and adipose tissue dysfunction to cancer (Avgerinos et al., 2019). BMI affects cancer risk through overabundance of visceral fat in obese individuals, this fat which surrounds the abdominal organs, plays an important role in the determinant of insulin resistance by secreting a considerable amount of pro-inflammatory markers, growth factors, free fatty acids, locally synthesized estrogens, hormone and adipocytokines which contributes to the development of cancer but also other diseases (Dalamaga et al., 2012). BMI also affects cancer risk through sex hormones biosynthesis. Obesity is known to induce fluctuations of reproductive hormone concentrations. The risk for certain gynaecological cancers such as endometrial, ovarian and postmenopausal breast cancer was also reported to be significantly increase with increasing concentrations of sex hormones including total estradiol, free estradiol, estrone, estrone sulfate, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and testosterone (Key et al., 2002) . Obesity and excessive adipose tissue increases the activity of the enzyme aromatase which leads to higher conversion rate of androgens to estradiol, resulting in higher level of estrogens which promotes tumorigenesis in endometrial tissue (Avgerinos et al., 2019). Epidemiological evidence reported 2 to 6 folds higher risk of endometrial cancer in association with obesity compared to normal BMI (Shaw et al., 2009) (Conroy et al., 2009). Consistently, we observed similar risk regarding endometrial cancer and obesity in our study.

Another mechanism is through alterations in adipocytokine pathophysiology. Adipose tissue, an active endocrine organ, has a major component known as the white adipose tissue, a metabolically active endocrine and secretory organ (Proença et al., 2014). In obese individuals, there is hypoxia of the adipose tissue from the surplus of cytokins and adipokines. This results in a chronic inflammatory state which affects the microenvironment and causes cellular perturbations, thereby facilitating cancer development and progression (Pérez-Hernández et al., 2014, Diedrich et al., 2015, Divella et al., 2016). Additional function of the adipose tissue is to release adiponectin and leptin into the bloodstream. Adiponectin synthesis is reduced (Cnop et al., 2003), while leptin synthesis is increased when there is excessive ectopic and visceral fat due to obesity (Avgerinos et al., 2019). Adiponectin is a hormone which has anti-inflammatory and insulin sensitizing properties while leptin is known to exerts pro-inflammatory actions which stimulates the production inflammatory cytokines such as of tumor necrosis factor- α (TNF-a),

interleukin (IL-1, IL-6, IL-12) and leukotriene B4 (Carbone et al., 2012) which increased the risk of cancer.

Insulin and Insuline-like growth factors (IGFs) plays also a significant part in the involvement of BMI in cancer mechanism. IGFs, a hormone which is similar in structure to insulin and plays an important role in growth, development and survival, is synthesized by almost any tissue in the organism (Moschos & Mantzoros, 2002). There have been epidemiological evidence that increased serum IGFs levels and altered circulation levels of their binding proteins are associated with an increased risk of developing several malignancies (Manousos et al., 1999, Renehan et al., 2004). Insulin is known to promote carcinogenesis directly and indirect by reducing the level of circulating IGFBP1 and IGFBP2 (two out of the six specific high-affinity binding proteins in the IGF system), consequently, the level of circulating IGF increases.

Physical activity has some direct and indirect effect on cancer risks. Evidence suggests that independently of body fatness, promoting physical activity can lead to health benefits that prevent cancer through mechanisms such as reduction of metabolic abnormalities, reduction of chronic low grade inflammation and reduction of endogenous sex hormones (Avgerinos et al., 2019). Randomized control trials and observational epidemiologic studies have shown that physical activity reduces plasma insulin and increases insulin sensitivity by lowering IGF-1 levels and increasing IGFBP-3 level (Thomas et al., 2017). A clinical study conducted by de Boer and colleagues demonstrated that long term physical activity exerts anti-inflammatory effects on a systemic level by reducing the level of pro-inflammatory biomarkers (de Boer et al., 2017). This study also showed that women that had high level of physical activity have statistically significant levels of reduction in free estradiols, estradiols and estrone, which are female sex hormones, while increasing the level of sex hormone-binding globulin (SHBG). SHBG is a glycoprotein which regulates the amount of free estrogens that are associated with the increased risk of hormone sensitive cancer (Friedenreich et al., 2021). Weight loss from physical activity is the reason for the effect of physical activity on sex hormones (Ennour-Idrissi et al., 2015). However, a combination of physical activity with caloric restrictions is most effective in producing changes to endrogenous hormones (de Roon et al., 2018). Physical activity is also said to reduce the amount of free testosterone and other androgens (Pasquali & Oriolo, 2019).

It has been suggested that physical activity impacts oxidative stress by affecting the balance between antioxidant and reactive oxygen species (ROS). ROS causes abnormalities in the

chromosomes, DNA damage and mutation in genes that suppress tumors (de Boer et al., 2017). Although acute physical activity increases oxidative stress, regular physical activity is reported to build up antioxidant defenses which are known to lower cancer risk (Nieman & Wentz, 2019, Friedenreich et al., 2021). Physical activity also indirectly impacts cancer risks by reducing adiposity (McTiernan, 2008) thereby exerting the mechanism mentioned for BMI in relation to adipose fat.

We found that maintaining a healthy BMI and a high level of physical activity is important in reducing the risk of overall cancer, being overweight increases the risk of cancer but increasing level of physical activity mitigates this risk. It is possible that obesity is a point where physical activity cannot be used to mitigate the excess risk of overall cancer. However, additional studies are needed to understand this hypothesis.

Our study has some limitations to be taken in consideration when interpreting these findings. First, although it is large, the E3N population is homogeneous and mainly consists of teachers, considered to be health conscious and leaner on average than French women in general. Our analyses are based on self-reported BMI, therefore bias could exist. Recent studies have shown good correlations between self-reported measurements of BMI and measurements by technicians. We used BMI as a measure of adiposity which is not the best metric indicator. BMI is inaccurate for evaluating older population, individuals with dense muscular composition and some population from specific area such as Asian descent. This is because BMI does not differentiate between lean mass and adipose tissue because of how it is calculated. Secondly, assessing physical activity in epidemiologic studies is difficult because of the complex nature of this lifestyle exposure, the lack of available gold standards to validate exposure assessments, and the need to rely on self-reports in large epidemiologic studies. Moreover, the complexity of assessing physical activity implies that each method of assessment may introduce a misclassification bias in the analysis. Finally, we did not conduct analyses by others anthropometric measurements or type of physical activity (sport, gardening and walking etc…). We used the exposures at baseline collected through a single questionnaire assessment, which could not consider exposure changes during follow-up.

Despite these limitations, our study has some strength which includes the prospective design, the large size of the cohort, the high rate of follow-up, histologic confirmation of cancer, and the detailed information available on potential confounders, including updated data on reproductive, menopausal status, and use of pills. This study is a large study that investigated the joint

association of two important factors such as BMI and physical activity and provides significant findings. The role of BMI and physical activity should be study jointly, as one entity, not individually to ensure a better evaluation of cancer burden related to weight and physical activity.

CONCLUSION AND PUBLIC HEALTH IMPLICATION

In conclusion, our findings suggests that overweight and obesity were associated with higher risk of cancer overall, whereas high physical activity was associated with lower risk of cancer. Specifically, obese women had a higher risk of colorectal and endometrial cancer compared with normal BMI women, while women with high level of physical activity had a lower risk of only breast cancer. In addition, we found that physical activity mitigated the risk of overall cancer especially in overweight participants, whereas this latter did not mitigate the effect in obese women.

This present study suggests that overweight or obese participants should be encouraged to increase their physical activity levels in order to reduce their risk to develop cancer. If confirmed, our findings may have important public health implications.

REFERENCES

Anand, P., Kunnumakara, A. B., Sundaram, C., Harikumar, K. B., Tharakan, S. T., Lai, O. S., Sung, B., & Aggarwal, B. B. (2008). Cancer is a preventable disease that requires major lifestyle changes. Pharmaceutical Research, 25(9), 2097–2116. https://doi.org/10.1007/s11095-008-9661-9

Arem, H., & Loftfield, E. (2018). Cancer Epidemiology : A Survey of Modifiable Risk Factors for Prevention and Survivorship. https://doi.org/10.1177/1559827617700600.

Arem, H., Park, Y., Pelser, C., Ballard-Barbash, R., Irwin, M. L., Hollenbeck, A., Gierach, G. L., Brinton, L. A., Pfeiffer, R. M., & Matthews, C. E. (2013). Prediagnosis body mass index, physical activity, and mortality in endometrial cancer patients. Journal of the National Cancer Institute, 105(5), 342–349. https://doi.org/10.1093/jnci/djs530

Arnold, M., Pandeya, N., Byrnes, G., G, P. A., Miranda, J. J., Romieu, I., & Dikshit, R. (2016). NIH Public Access. 16(1), 36–46. https://doi.org/10.1016/S1470-2045(14)71123-4.Global

Avgerinos, K. I., Spyrou, N., Mantzoros, C. S., & Dalamaga, M. (2019). Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism: Clinical and Experimental, 92, 121–135. https://doi.org/10.1016/j.metabol.2018.11.001

Bellocco, R., Marrone, G., Ye, W., Nyrén, O., Adami, H. O., Mariosa, D., & Lagerros, Y. T. (2016). A prospective cohort study of the combined effects of physical activity and anthropometric measures on the risk of post-menopausal breast cancer. European Journal of Epidemiology, 31(4), 395–404. https://doi.org/10.1007/s10654-015-0064-z

Cannon, G. (2008). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Choice Reviews Online, 45(09), 45-5024-45–5024. https://doi.org/10.5860/choice.45-5024

Carbone, F., La Rocca, C., & Matarese, G. (2012). Immunological functions of leptin and adiponectin. Biochimie, 94(10), 2082–2088. https://doi.org/10.1016/j.biochi.2012.05.018

Clavel-Chapelon, F. (2015). Cohort Profile: The French E3N Cohort Study. International Journal of Epidemiology, 44(3), 801–809. https://doi.org/10.1093/ije/dyu184

Cnop, M., Havel, P. J., Utzschneider, K. M., Carr, D. B., Sinha, M. K., Boyko, E. J., Retzlaff, B. M., Knopp, R. H., Brunzell, J. D., & Kahn, S. E. (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: Evidence for independent roles of age and sex. Diabetologia, 46(4), 459–469. https://doi.org/10.1007/s00125-003-1074-z

Colditz, G. A., Feskanich, D., Chen, W. Y., Hunter, D. J., & Willett, W. C. (2003). Physical activity and risk of breast cancer in premenopausal women. 89(May 2014). https://doi.org/10.1038/sj.bjc.6601175

Colonna, M., Boussari, O., Cowppli-Bony, A., Delafosse, P., Romain, G., Grosclaude, P., & Jooste, V. (2018). Time trends and short term projections of cancer prevalence in France. Cancer Epidemiology, 56(April), 97–105. https://doi.org/10.1016/j.canep.2018.08.001

Colonna, Marc, Danzon, A., Delafosse, P., Mitton, N., Bara, S., Bouvier, A. M., Ganry, O., Guizard, A. V., Launoy, G., Molinie, F., Sauleau, E. A., Schvartz, C., Velten, M., Grosclaude, P., & Tretarre, B. (2008). Cancer prevalence in France: Time trend, situation in 2002 and extrapolation to 2012. European Journal of Cancer, 44(1), 115–122. https://doi.org/10.1016/j.ejca.2007.10.022

Conroy, M. B., Sattelmair, J. R., Cook, N. R., Manson, J. E., Buring, J. E., & Lee, I. M. (2009). Physical activity, adiposity, and risk of endometrial cancer. Cancer Causes and Control, 20(7), 1107–1115. https://doi.org/10.1007/s10552-009-9313-3

Cowppli-Bony, A., Colonna, M., Ligier, K., Jooste, V., Defossez, G., Monnereau, A., Amadeo, B., Arveux, P., Baldi, I., Bara, S., Bouvier, A. M., Bouvier, V., Clavel, J., Coureau, G., Dalmeida, T., Daubisse-Marliac, L., Delafosse, P., Deloumeaux, J., Grosclaude, P., … Woronoff, A. S. (2019). Descriptive epidemiology of cancer in metropolitan France: Incidence, survival and prevalence. Bulletin Du Cancer, 106(7–8), 617–634. https://doi.org/10.1016/j.bulcan.2018.11.016

Dalamaga, M., Diakopoulos, K. N., & Mantzoros, C. S. (2012). The role of adiponectin in cancer: A review of current evidence. Endocrine Reviews, 33(4), 547–594. https://doi.org/10.1210/er.2011-1015

Dartois, L., Fagherazzi, G., Boutron-Ruault, M. C., Mesrine, S., & Clavel-Chapelon, F. (2014). Association between five lifestyle habits and cancer risk: Results from the E3N cohort. Cancer Prevention Research, 7(5), 516–525. https://doi.org/10.1158/1940-6207.CAPR-13-0325

de Boer, M. C., Wörner, E. A., Verlaan, D., & van Leeuwen, P. A. M. (2017). The Mechanisms and Effects of Physical Activity on Breast Cancer. Clinical Breast Cancer, 17(4), 272–278. https://doi.org/10.1016/j.clbc.2017.01.006

de Roon, M., May, A. M., McTiernan, A., Scholten, R. J. P. M., Peeters, P. H. M., Friedenreich, C. M., & Monninkhof, E. M. (2018). Effect of exercise and/or reduced calorie dietary interventions on breast cancer-related endogenous sex hormones in healthy postmenopausal women. Breast Cancer Research, 20(1), 1–16. https://doi.org/10.1186/s13058-018-1009-8

Diedrich, J., Gusky, H. C., & Podgorski, I. (2015). Adipose tissue dysfunction and its effects on tumor metabolism. Hormone Molecular Biology and Clinical Investigation, 21(1), 17–41. https://doi.org/10.1515/hmbci-2014-0045

Dirx, M. J. M., Voorrips, L. E., Alexandra Goldbohm, R., & Van Den Brandt, P. A. (2001). Baseline recreational physical activity, history of sports participation, and postmenopausal breast carcinoma risk in The Netherlands Cohort Study. Cancer, 92(6), 1638–1649. https://doi.org/10.1002/1097-0142(20010915)92:6<1638::AID-CNCR1490>3.0.CO;2-Q

Divella, R., De Luca, R., Abbate, I., Naglieri, E., & Daniele, A. (2016). Obesity and cancer: The role of adipose tissue and adipo-cytokines-induced chronic inflammation. Journal of Cancer, 7(15), 2346–2359. https://doi.org/10.7150/jca.16884

Ennour-Idrissi, K., Maunsell, E., & Diorio, C. (2015). Effect of physical activity on sex hormones in women: A systematic review and meta-analysis of randomized controlled trials. Breast Cancer Research, 17(1), 1–11. https://doi.org/10.1186/s13058-015-0647-3

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. International Journal of Cancer, 136(5), E359–E386. https://doi.org/10.1002/ijc.29210

Friedenreich, C. M., Ryder-Burbidge, C., & McNeil, J. (2021). Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Molecular Oncology, 15(3), 790–800. https://doi.org/10.1002/1878-0261.12772

Hassanpour, S. H., & Dehghani, M. (2017). Review of cancer from perspective of molecular. Journal of Cancer Research and Practice, 4(4), 127–129. https://doi.org/10.1016/j.jcrpr.2017.07.001

Holmes, M. D., & Willett, W. C. (2011). NIH Public Access. 170(19), 1758–1764. https://doi.org/10.1001/archinternmed.2010.363.Physical

IARC. (2020). World cancer report 2020. In World Health Organization. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

Kamangar, F., Dores, G. M., & Anderson, W. F. (2006). Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. Journal of Clinical Oncology, 24(14), 2137–2150. https://doi.org/10.1200/JCO.2005.05.2308

Katzke, V. A., Kaaks, R., & Kühn, T. (2015). Lifestyle and cancer risk. Cancer Journal (United States), 21(2), 104–110. https://doi.org/10.1097/PPO.0000000000000101

Key, T. J., Appleby, P., Barnes, I., Reeves, G., Dorgan, J. F., Longcope, C., Franz, C., Stanczyk, F. Z., Chang, L. C., Stephenson, H. E., Falk, R. T., Kahle, L., Miller, R., Tangrea, J. A., Campbell, W. S., Schatzkin, A., Allen, D. S., Fentiman, I. S., Moore, J. W., … Miller, S. R. (2002). Endogenous sex hormones and breast cancer in postmenopausal women: Reanalysis of nine prospective studies. Journal of the National Cancer Institute, 94(8), 606–616. https://doi.org/10.1093/jnci/94.8.606

Lancet. (2016). Trends in adult body-mass index in 200 countries from 1975 to 2014 : a pooled analysis of 1698 population-based measurement studies with 19 · 2 million participants. The Lancet, 387(10026), 1377–1396. https://doi.org/10.1016/S0140-6736(16)30054-X

Maliniak, M. L., Gapstur, S. M., Mccullough, L. E., Rees, E., Mia, P., Um, C. Y., Guinter, M. A., Flanders, W. D., & Patel, A. V. (2020). Joint associations of physical activity and body mass index with the risk of established excess body fatness - related cancers among postmenopausal women. Cancer Causes & Control, 0123456789. https://doi.org/10.1007/s10552-020-01365-2

Manousos, O., Souglakos, J., Bosetti, C., Tzonou, A., Chatzidakis, V., Trichopoulos, D., Adami, H. O., & Mantzoros, C. (1999). IGF-I and IGF-II in relation to colorectal cancer. International Journal of Cancer, 83(1), 15–17. https://doi.org/10.1002/(SICI)1097-0215(19990924)83:1<15::AID-IJC4>3.0.CO;2-Y

McTiernan, A. (2008). Mechanisms linking physical activity with cancer. Nature Reviews Cancer, 8(3), 205–211. https://doi.org/10.1038/nrc2325

Mctiernan, A., Friedenreich, C. M., Katzmarzyk, P. T., Powell, K. E., Macko, R., Buchner, D., Pescatello, L. S., Bloodgood, B., Tennant, B., Vaux-Bjerke, A., George, S. M., Troiano, R. P., & Piercy, K. L. (2019). Physical Activity in Cancer Prevention and Survival: A Systematic Review. Medicine and Science in Sports and Exercise, 51(6), 1252–1261. https://doi.org/10.1249/MSS.0000000000001937

McTiernan, A., Kooperberg, C., White, E., Wilcox, S., Coates, R., Adams-Campbell, L. L., Woods, N., & Ockene, J. (2003). Recreational Physical Activity and the Risk of Breast Cancer in Postmenopausal Women: The Women's Health Initiative Cohort Study. Journal of the American Medical Association, 290(10), 1331–1336. https://doi.org/10.1001/jama.290.10.1331

Micheli, A., Mugno, E., Krogh, V., Quinn, M. J., Coleman, M., Hakulinen, T., Gatta, G., Berrino, F., & Capocaccia, R. (2002). Cancer prevalence in European registry areas. Annals of Oncology, 13(6), 840–865. https://doi.org/10.1093/annonc/mdf127

Moore, S. C., Lee, I. M., Weiderpass, E., Campbell, P. T., Sampson, J. N., Kitahara, C. M., Keadle, S. K., Arem, H., De Gonzalez, A. B., Hartge, P., Adami, H. O., Blair, C. K., Borch, K. B., Boyd, E., Check, D. P., Fournier, A., Freedman, N. D., Gunter, M., Johannson, M., … Patel, A.

V. (2016). Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Internal Medicine, 176(6), 816–825. https://doi.org/10.1001/jamainternmed.2016.1548

Moore, S. C., Lee, I., Weiderpass, E., Campbell, P. T., Sampson, J. N., Kitahara, C. M., Keadle, S. K., Arem, H., Gonzalez, A. B. De, Hartge, P., Adami, H., Blair, C. K., Borch, K. B., Boyd, E., Check, D. P., Fournier, A., Freedman, N. D., Gunter, M., Johannson, M., … Patel, A. V. (2016). Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. 20850, 1–10. https://doi.org/10.1001/jamainternmed.2016.1548

Moschos, S. J., & Mantzoros, C. S. (2002). The role of the IGF system in cancer: From basic to clinical studies and clinical applications. Oncology, 63(4), 317–332. https://doi.org/10.1159/000066230

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global Cancer Statistics, 2002. CA: A Cancer Journal for Clinicians, 55(2), 74–108. https://doi.org/10.3322/canjclin.55.2.74

Pasquali, R., & Oriolo, C. (2019). Obesity and Androgens in Women. Frontiers of Hormone Research, 53, 120–134. https://doi.org/10.1159/000494908

Pérez-Hernández, A. I., Catalán, V., Gómez-Ambrosi, J., Rodríguez, A., & Frühbeck, G. (2014). Mechanisms linking excess adiposity and carcinogenesis promotion. Frontiers in Endocrinology, 5(MAY), 1–17. https://doi.org/10.3389/fendo.2014.00065

Peters, T. M., Schatzkin, A., Gierach, G. L., Moore, S. C., James, V., Jr, L., Wareham, N. J., Ekelund, U., Hollenbeck, A. R., & Michael, F. (2010). NIH Public Access. 18(1), 289–296. https://doi.org/10.1158/1055-9965.EPI-08-0768.Physical

Proença, A. R. G., Sertié, R. A. L., Oliveira, A. C., Campaña, A. B., Caminhotto, R. O., Chimin, P., & Lima, F. B. (2014). New concepts in white adipose tissue physiology. Brazilian Journal of Medical and Biological Research, 47(3), 192–205. https://doi.org/10.1590/1414-431X20132911

Ratnasinghe, L. D., Modali, R. V, Seddon, M. B., Lehman, A., Ratnasinghe, L. D., Modali, R. V, Seddon, M. B., Ratnasinghe, L. D., Modali, R. V, Seddon, M. B., & Lehman, T. A. (2010). Physical Activity and Reduced Breast Cancer Risk : A Multinational Study Physical Activity and Reduced Breast Cancer Risk : A Multinational Study. 5581. https://doi.org/10.1080/01635580903441295

Renehan, A. G., Zwahlen, M., Minder, C., O'Dwyer, S. T., Shalet, S. M., & Egger, M. (2004). Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: Systematic review and meta-regression analysis. Lancet, 363(9418), 1346–1353. https://doi.org/10.1016/S0140-6736(04)16044-3

Rezende, L. F. M. de, Garcia, L. M. T., Mielke, G. I., Lee, D. H., Wu, K., Giovannucci, E., & Eluf-Neto, J. (2018). Preventable fractions of colon and breast cancers by increasing physical activity in Brazil: perspectives from plausible counterfactual scenarios. Cancer Epidemiology, 56(June), 38–45. https://doi.org/10.1016/j.canep.2018.07.006

Rezende, L. F. M. de, Sá, T. H. De, Markozannes, G., Rey-lópez, J. P., Lee, I., Tsilidis, K. K., Ioannidis, J. P. A., & Eluf-neto, J. (2018). Physical activity and cancer : an umbrella review of the literature including 22 major anatomical sites and 770 000 cancer cases. 826–833. https://doi.org/10.1136/bjsports-2017-098391

Secretan, B. L., Ph, D., Scoccianti, C., Ph, D., Loomis, D., & Ph, D. (2016). Spe ci a l R e p or t Body Fatness and Cancer — Viewpoint of the IARC Working Group.

Shaw, E., Farris, M., McNeil, J., & Friedenreich, C. (2009). Obesity and Endometrial cancer. In Biochemist (Vol. 31, Issue 4). Springer. https://doi.org/10.1042/bio03104053

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 0(0), 1–41. https://doi.org/10.3322/caac.21660

Suzuki, S., Kojima, M., Tokudome, S., Mori, M., Sakauchi, F., Fujino, Y., Wakai, K., Lin, Y., Kikuchi, S., & Tamakoshi, K. (2008). Effect of Physical Activity on Breast Cancer Risk : Findings of the Japan Collaborative Cohort Study. 17(December), 3396–3402. https://doi.org/10.1158/1055-9965.EPI-08-0497

Thomas, R. J., Kenfield, S. A., & Jimenez, A. (2017). Exercise-induced biochemical changes and their potential influence on cancer: A scientific review. British Journal of Sports Medicine, 51(8), 640–644. https://doi.org/10.1136/bjsports-2016-096343

Thune, I., Tormod, B., Lund, E., & Gaard, M. (1997). Physical activity and the risk of breast cancer. Clinical Journal of Sport Medicine, 7(4), 315. https://doi.org/10.1097/00042752-199710000-00013

Whiteman, D. C., & Wilson, L. F. (2016). The fractions of cancer attributable to modifiable factors: A global review. Cancer Epidemiology, 44, 203–221. https://doi.org/10.1016/j.canep.2016.06.013

Wilson, L. F., Baade, P. D., Green, A. C., Jordan, S. J., Kendall, B. J., Neale, R. E., Olsen, C. M., Youlden, D. R., Webb, P. M., & Whiteman, D. C. (2019). The impact of changing the prevalence of overweight/obesity and physical inactivity in Australia: An estimate of the proportion of potentially avoidable cancers 2013–2037. International Journal of Cancer, 144(9), 2088–2098. https://doi.org/10.1002/ijc.31943

Wiseman, M. (2008). The Second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Proceedings of the Nutrition Society, 67(3), 253–256. https://doi.org/10.1017/S002966510800712X

Yang, D., Ph, D., Bernstein, L., Ph, D., Wu, A. H., & Ph, D. (1998). Physical Activity and Breast Cancer Risk among Asian-American Women in Los Angeles A Case – Control Study. https://doi.org/10.1002/cncr.11364

APPENDICES

Appendix 1: Baseline characteristics of study participants according to physical activity, n=90,849, E3N cohort, 1990–2014

	Physical Activity category			
	Quartile 1 [0.0 – 26.50 MET-h/week]	Quartile 2 [26.6 – 38.4 MET-h/week]	Quartile 3 [38.5 – 54.9 MET-h/week]	Quartile 4 [55.1 – 223.8 MET-h/week]
CHARACTERISTICS	(n= 22,530)	(n= 22,875)	(n= 22,546)	(n= 22,898)
Age at baseline Mean(SD)	49.05 (6.40)	48.77 (6.35)	48.96 (6.57)	50.25 (7.05)
Year of birth (%)				
≤1930	8.45	7.83	9.11	13.39
1931-1935	12.58	11.90	12.41	16.55
1936- 1940	21.29	20.57	19.73	18.87
1941-1945	26.72	25.73	24.84	22.23
≥1946	30.97	33.97	33.90	28.97
Educational level (%)				
<12 years	13.52	13.46	15.80	21.84
12 - 14 years	47.94	50.24	51.47	49.27
>14 years	38.54	36.30	32.72	28.89
Smoking status (%)				
Non smoker	52.87	53.46	54.35	56.16
Ex- smoker	31.50	31.77	30.70	29.46
Current smoker	15.63	14.77	14.96	14.39
BMI category (%)				
Underweight	6.68	6.16	5.61	5.81
Normal weight	73.96	77.33	77.91	76.93
Over weight	15.33	13.80	13.99	14.34
Obese	4.04	2.71	2.49	2.92
Marital status (%)				
Single	21.23	18.20	16.23	14.52
Married	74.75	77.81	80.18	81.72
Missing	4.02	3.99	3.58	3.76
Dietary score (%)				
Quartile 1	19.28	18.58	17.75	16.63
Quartile 2	15.78	15.49	15.64	14.92
Quartile 3	21.13	22.45	23.15	23.05

Quartile 4	19.17	21.72	22.03	22.98
Missing	24.65	21.75	21.42	22.41
Family history of cancer (%)				
No	21.06	19.51	19.40	19.69
Yes	78.94	80.49	80.60	80.31
Hypertension (%)				
No	85.75	85.40	85.23	85.71
Yes	14.25	14.60	14.77	14.29
Diabetes (%)				
No	95.68	96.32	96.35	95.91
Yes	4.32	3.68	3.65	4.09
Menopause status (%)				
Pre-menopausal	3.26	3.00	2.71	2.89
menopausal type unknown	5.14	4.86	5.20	4.92
Menopausal, naturally	83.25	83.71	83.35	82.69
Menopausal artificially	8.34	8.41	8.72	9.47
Never mensturated	0.02	0.02	0.02	0.03
Age at menarche (%)				
<13 years	46.51	46.16	45.49	43.69
13 -14 years	43.57	44.02	44.47	44.70
>14 years	9.92	9.82	10.04	11.61
Age of first birth (%)				
<23 years	38.81	38.70	39.58	42.04
23 - 25 years	28.21	29.30	31.05	31.30
>25 years	32.99	32.00	29.38	26.66
Breastfeed (%)				
No	32.83	31.95	30.26	28.71
Yes	67.17	68.05	69.74	71.29
Ever use of menopausal hormone therapy (%)				
No	69.38	70.73	70.74	69.53
Yes	18.86	18.96	18.93	19.93
Missing	11.75	10.31	10.33	10.53
Ever use of oral contraceptives (%)				
No	46.03	41.32	42.14	48.07
Yes	53.97	58.68	57.86	51.93

Appendix 2: Hazard ratios and 95% CI for the association between BMI and risk of cancers, results from unadjusted and adjusted cox regression models, n=90,018, E3N cohort, 1990–2014

	BMI CATEGORY				
	Underweight (n=3,835)	Normal (n=70,202)	Overweight (n=13,187)	Obese (n=2,794)	P-trend
All cancer					
Cases, n	635	12,558	2,467	520	
Model 1	0.99 (0.91-1.07)	1	1.05 (1.01-1.10)	1.11 (1.02-1.21)	0.002
Model 2	0.97 (0.90-1.05)	1	1.08 (1.03-1.13)	1.20 (1.10-1.31)	<0.0001
Model 3	0.97 (0.90-1.05)	1	1.08 (1.03-1.13)	1.20 (1.09-1.31)	<0.0001
Breast cancer					
Cases, n	323	6,376	1,151	215	
Model 1	0.97 (0.86-1.08)	1	1.00 (0.94-1.07)	0.93 (0.81-1.06)	0.7172
Model 2	0.95 (0.85-1.06)	1	1.03 (0.97-1.10)	1.03 (0.89-1.18)	0.1896
Model 3	0.95 (0.85-1.06)	1	1.03 (0.97-1.08)	1.09 (0.89-1.17)	0.2491
Lung cancer					
Cases, n	18	409	77	9	
Model 1	0.91 (0.56-1.45)	1	0.93 (0.73-1.19)	0.56 (0.29-1.08)	0.2085
Model 2	0.86 (0.53-1.38)	1	0.93 (0.72-1.20)	0.54 (0.27-1.05)	0.2423
Model 3	0.86 (0.54-1.38)	1	0.93 (0.73-1.20)	0.55 (0.28-1.07)	0.2596
Ovarian cancer					
Cases, n	19	430	82	22	
Model 1	0.85 (0.57-1.35)	1	1.02 (0.81-1.30)	1.37 (0.89-2.10)	0.1931
Model 2	0.84 (0.53-1.33)	1	1.01 (0.79-1.28)	1.33 (0.85-2.07)	0.2635
Model 3	0.84 (0.53-1.33)	1	1.01 (0.79-1.29)	1.34 (0.86-2.09)	0.2478
Colorectal cancer					
Cases, n	44	803	178	40	
Model 1	1.14 (0.89-1.54)	1	1.09 (0.92-1.28)	1.25 (0.91-1.72)	0.2648
Model 2	1.12 (0.82-1.52)	1	1.12 (0.95-1.32)	1.39 (1.00-1.92)	0.0894
Model 3	1.12 (0.83-1.52)	1	1.12 (0.95-1.33)	1.39 (1.01-1.93)	0.0829
Endometrial cancer					
Cases, n	15	428	125	55	
Model 1	0.70 (0.42-1.18)	1	1.50 (1.23 1.83)	3.32 (2.51-4.41)	<0.0001
Model 2	0.68 (0.41-1.14)	1	1.52(1.24-1.87)	3.53 (2.62-4.74)	<0.0001
Model 3	0.68 (0.41-1.14)	1	1.52(1.24-1.86)	3.51 (2.61-4.72)	<0.0001
Liver cancer					
Cases, n	3	40	19	6	
Model 1	1.67 (0.52-5.41)	1	2.07 (1.19-3.60)	3.37 (1.42-7.97)	0.0026
Model 2	1.83 (0.56-5.96)	1	1.48 (0.83-2.63)	1.48 (0.58-3.74)	0.3663
Model 3	1.83 (0.56-5.95)	1	1.49 (0.84-2.65)	1.51 (0.60-3.84)	0.3431

Melanoma skin cancer					
Cases, n	44	788	143	28	
Model 1	1.07 (0.79-1.45)	1	1.01 (0.85-1.21)	1.00 (0.68-1.46)	0.9175
Model 2	1.08 (0.80-1.47)	1	1.05 (0.88-1.26)	1.11 (0.75-1.63)	0.6712
Model 3	1.08 (0.80-1.47)	1	1.05 (0.88-1.26)	1.10 (0.75-1.62)	0.6760
Blood cancer					
Cases, n	28	456	107	18	
Model 1	1.26 (0.86-1.85)	1	1.19 (0.96-1.47)	1.02 (0.64-1.64)	0.5539
Model 2	1.26 (0.86-1.85)	1	1.19 (0.96-1.48)	1.03 (0.64-1.67)	0.5553
Model 3	1.26 (0.86-1.85)	1	1.19 (0.96-1.47)	1.02 (0.64-1.65)	0.5900
Thyroid cancer					
Cases, n	13	429	96	559	
Model 1	0.55 (0.32-0.96)	1	1.33 (1.06-1.66)	1.42 (0.91-2.20)	0.0004
Model 2	0.55 (0.31-0.95)	1	1.32 (1.05-1.65)	1.47 (0.94-2.30)	0.0004
Model 3	0.55 (0.31-0.95)	1	1.32 (1.05-1.65)	1.47 (0.93-2.30)	0.0005
Stomach cancer					
Cases, n	4	66	17	5	
Model 1	1.25 (0.45-3.43)	1	1.26 (0.74-2.16)	1.92 (0.77-4.77)	0.2247
Model 2	1.22 (0.44-3.36)	1	1.25 0.72-2.15)	2.05 (0.80-5.26)	0.2186
Model 3	1.22 (0.44-3.36)	1	1.25 (0.73-2.16)	2.06 (0.81-5.30)	0.2132

Model 1: Unadjusted model

Model 2: Adjusted for Education level, smoking status, use of oral contraceptive, use of menopausal hormonal therapy, family history of cancer, marital status, age of first full term pregnancy, age of menarche, menopausal status, breastfeeding, diabetes and dietary score

Model 3: Adjusted for same co-variables in model 2 including physical activity

Appendix 3: Hazard ratios and 95% CI for the association between physical activity and risk of cancers, results from unadjusted and adjusted cox regression models, n=90,849, E3N cohort, 1990–2014

	Physical Activity category				
	Quartile 1 [0.0 – 26.50 MET-h/week] (n=22,530)	Quartile 2 [26.6 – 38.4 MET-h/week] (n=22,875)	Quartile 3 [38.5 – 54.9 MET-h/week] (n=22,546)	Quartile 4 [55.1 – 223.8 MET-h/week] (n=22,898)	P-trend
All cancer					
Cases, n	4,160	4,147	4,009	4,016	
Model 1	1	0.97 (0.93-1.02)	0.95 (0.91-0.99)	0.92 (0.88-0.96)	<0.0001
Model 2	1	0.98 (0.93-1.02)	0.96 (0.92-1.00)	0.93 (0.89-0.97)	0.0006
Model 3	1	0.98 (0.94-1.02)	0.96 (0.92-1.00)	0.93 (0.89-0.97)	0.0012
Breast cancer					
Cases, n	2,155	2,106	2,027	1,829	
Model 1	1	0.95 (0.90- 1.01)	0.93 (0.88-0.99)	0.83 (0.78-0.88)	<0.0001
Model 2	1	0.95 (0.90-1.01)	0.94 (0.89-1.00)	0.85 (0.79-0.90)	<0.0001
Model 3	1	0.96 (0.90-1.01)	0.94 (0.89-1.00)	0.85 (0.80-0.90)	<0.0001
Lung cancer					
Cases, n	113	132	130	138	
Model 1	1	1.15 (0.89-1.47)	1.13 (0.88-1.45)	1.11 (0.86-1.42)	0.4932
Model 2	1	1.19 (0.92-1.53)	1.19 (0.92-1.53)	1.17 (0.91-1.51)	0.2493
Model 3	1	1.18 (0.92-1.51)	1.18 (0.92-1.51)	1.16 (0.91-1.50)	0.2776
Ovarian cancer					
Cases, n	130	135	142	149	
Model 1	1	1.01 (0.80-1.29)	1.07 (0.85-1.36)	1.08 (0.86-1.37)	0.4323
Model 2	1	1.03 (0.81-1.31)	1.10 (0.86-1.39)	1.10 (0.87-1.40)	0.3670
Model 3	1	1.03 (0.81-1.31)	1.10 (0.87-1.40)	1.10 (0.87-1.40)	0.3568
Colorectal cancer					
Cases, n	252	270	250	312	
Model 1	1	1.05 (0.89 1.25)	0.98 (0.82-1.16)	1.11 (0.94-1.31)	0.3469
Model 2	1	1.06 (0.89-1.26)	0.98 (0.83-1.17)	1.11 (0.94-1.32)	0.3232
Model 3	1	1.07 (0.90-1.27)	0.99 (0.83-1.18)	1.13 (0.95-1.33)	0.2845
Endometrial cancer					
Cases, n	167	145	170	147	
Model 1	1	0.85 (0.68-1.06)	1.00 (0.81-1.24)	0.81 (0.65-1.01)	0.1949
Model 2	1	0.87 (0.69-1.08)	1.03 (0.83-1.27)	0.83 (0.66-1.04)	0.2896
Model 3	1	0.89 (0.72-1.12)	1.06 (0.86-1.32)	0.86 (0.69-1.08)	0.4549
Liver cancer					
Cases, n	12	16	17	22	
Model 1	1	1.33 (0.63-2.81)	1.39 (0.66-2.90)	1.54 (0.76-3.12)	0.2483
Model 2	1	1.42 (0.67-3.00)	1.45 (0.69-3.04)	1.55 (0.76-3.16)	0.2596
Model 3	1	1.42 (0.67-3.01)	1.47 (0.70-3.09)	1.57 (0.77-3.20)	0.2407

Melanoma skin cancer					
Cases, n	247	253	248	266	
Model 1	1	0.99 (0.84-1.18)	0.99 (0.83-1.18)	1.04 (0.87-1.24)	0.6954
Model 2	1	0.98 (0.82-1.16)	0.97 (0.81-1.15)	1.02 (0.86-1.22)	0.8436
Model 3	1	0.98 (0.82-1.17)	0.97 (0.81-1.15)	1.02 (0.86-1.22)	0.8279
Blood cancer					
Cases, n	164	161	142	150	
Model 1	1	0.96 (0.77-1.20)	0.85 (0.68-1.07)	0.83 (0.67-1.04)	0.0617
Model 2	1	0.96 (0.77-1.19)	0.85 (0.68-1.07)	0.83 (0.67-1.04)	0.0650
Model 3	1	0.96 (0.77-1.20)	0.85 (0.68-1.07)	0.84 (0.67-1.05)	0.0721
Thyroid cancer					
Cases, n	143	155	138	132	
Model 1	1	1.05 (0.83-1.31)	0.95 (0.75-1.20)	0.93 (0.73-1.18)	0.4039
Model 2	1	1.05 (0.84-1.32)	0.95 (0.75-1.20)	0.91 (0.72-1.16)	0.3236
Model 3	1	1.06 (0.84-1.33)	0.96 (0.76-1.21)	1.00 (0.72-1.17)	0.3592
Stomach cancer					
Cases, n	23	18	27	95	
Model 1	1	0.77 (0.41-1.42)	1.15 (0.66-2.00)	1.05 (0.60-1.83)	0.5717
Model 2	1	0.76 (0.41-1.41)	1.12 (0.64-1.96)	1.01 (0.58-1.77)	0.6631
Model 3	1	0.77 (0.42-1.43)	1.15 (0.66-2.00)	1.03 (0.59-1.81)	0.6174

Model 1: Unadjusted model

Model 2: Adjusted for Education level, smoking status, use of oral contraceptive, use of menopausal hormonal therapy, family history of cancer, marital status, age of first full term pregnancy, age of menarche, menopausal status, breastfeeding, diabetes and dietary score

Model 3: Adjusted for same co-variables in model 2 including BMI

Appendix 4: Summary table of studies on association between BMI and physical activity and some specific cancer types.

Author, Year , Country	**Study name, characteristics** ***Cases/Control, Study size, Follow-up (years)***	**Exposure assessment**	**Outcome**	**Comparison**	**RR (95%CI)**	**Adjustment factors**
Aleksandrova et al 2017	EPIC cohort, A prospective cohort study including 366,521 women and 153,457 men aged 25 to 70 years from 23 study centers in 10 European countries (1992-2000). *713/713* *(Nested case-control)* *study n=1426* *cohort N=519,978.*	Self-reported	Colon cancer	Not clearly stated	Mediating factors - High Physical Activity: BMI, kg/m2 0.06 [-0.14, 0.00]	Age, sex, study centre, follow-up time since blood collection, time of the day at blood collection and fasting status; menopausal status, phase of menstrual cycle at blood collection hormonal replacement therapy use. Education, smoking status, alcohol intake, fruit and vegetable intake, fish and shellfish intake, fibre intake, red and processed meat intake (g/day) and high physical activity.
Arem et al 2012	National Institutes of Health (NIH)–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study Cohort. Female Members of AARP (aged 50-71). *1400 cases (N=197,128)*	Self-reported Baseline and follow up questionnaire	Endometrial cancer	<u>BMI</u>= WHO classification <u>MVPA</u> (never, rarely, <1 hour/ week, 1–3, 4–7, >7.	Obese vs inactive (HR = 2.05, 95% CI = 1.11 to 3.77)	Tumor grade, tumor stage, surgery, chemotherapy, race, family history of breast cancer, diabetes, and smoking status. Physical.

Bellocco et al 2016	The National March, national fund raising event arranged by the Swedish Cancer Society in almost 3600 Swedish cities and villages in September 1997. *609 cases (N=19,196)* *193,983 perosn years*	Self-reported Baseline and follow up questionnaire	Breast cancer	<u>BMI</u> 18.5– < 25(normal), 25– < 30 (overweight), ≥ 30 kg/m2 (obese) (WHO classification) <u>TPA</u> ≥ 38.2 (high) 31.2 - 38.1 (Medium) <31.2 (Low)	<u>PA vs Obese BMI</u> High - 1.36 [0.70, 2.65] Medium - 1.72 [1.00, 2.97] Low - 2.07 [1.31, 3.25]	Age at enrollment, cigarette smoking status, alcohol drinking, use of vitamin and mineral supplements, education level, contraceptive pill use, hormonal replacement therapy, age at menarche, number of children, age at first full-term pregnancy and childlessness.
Breslow et al 2001	The Epidemiological Follow-up Study (NHEFS) of the First National Health and Nutrition Examination Survey. 24–75 years when interviewed in 1971–1975. *138 cases (N=6160)*	In- person interview and medical examination survey of the civilian	Breast cancer	<u>BMI</u> <25.1 ≥25.1 <u>Activity level (Recreational)</u> Consistently low Moderate/inconsistent Consistently high	Not statistically significant	Height, BMI at age 25 years, adult weight change (age 25 years to age at 1982–1984 interview), education, age at menarche, parity, menstrual status, and family history of breast cancer.

Coldtz et al 2003	Nurses' Health Study II. Female registered nurses between 25 and 42 years of age and living within 14 US states. *110,468* *(849 cases).*	Self-reported: Questionnaire	Breast cancer	<u>BMI</u> 18.5– < 25, 25– < 29.9 , ≥ 30 kg/m2 <u>RPA</u> <3.0 (METh/week) 3.0–8.9 9.0–17.9 18.0–26.9 ≥27.0	Not statistically significant.	Age, BMI, height, alcohol intake, age at menarche, parity, age at first birth, history of benign breast disease, mother/sister with breast cancer.
Conroy et al 2009	Women's Health Study Eligible subjects were healthy US Female health professionals. *264 cases (N=32,642)* *8.8 years.*	Self-reported Baseline and follow up questionnaire	Endometrial cancer	<u>Total Energy Expenditure</u> <2.7 2.7–8.4 8.4–20.4 ≥20.4 <u>BMI</u> <22.5 22.5–24.9 25.0–29.9 30.0+	Overweight, inactive 1.85 (1.26–2.72) Overweight, active 1.60 (1.01–2.54) Normal weight, inactive 1.17 (0.77–1.77) Normal weight, active 1.00 (ref)	Adjusted for age, physical activity, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, and menopausal status. *Additionally adjusted for BMI.

D'Avanzo et al 1996	A multicentric case-control study on breast cancer conducted between June 1991 and February 1994 in Italy. *2569/2588*	Interview	Breast cancer	<u>BMI</u> <23.3 233-26.5 ≥26.6 <u>PA</u> (h/week) <2, 2-4, 5-7, >7	0.76(0.5-1.0) 0.74 (0.5-1.0) 0.62 (0.4-1.0) p-trend 4.30	Age, center, age at menarche, menopausal status, age at menopause. calorie intake, previous benign breast disease, and history of breast cancer in first-degree relatives.
Friedenreich et al 2001	Population-based case-control study Alberta, Canada, 1995 - 1997. *1233/1237*	In-person interviews	Breast cancer	<u>BMI</u> Low (<25 kg/m2) Medium (≥25–<30 kg/m2) High (≥30 kg/m2) <u>TPA</u> METh/week/year 0–<86.6 86.6–<108.3 108.3–<134.9 ≥134.9	Not statistically significant	Age, waist-hip ratio (in quartiles), educational level (in quintiles), ever use of hormone replacement therapy, ever diagnosed with benign breast disease, first-degree family history of breast cancer, current cigarette smoker, and ever alcohol consumption.

Hirose et al 2002	Aichi Cancer Center (HERPACC) study. *2376/18,977*	Self-administered questionnaire	Breast cancer	<u>BMI</u> Low <22 Medium 22–25 High ≥25 <u>PA</u> none occasional 3–4 times/mo ≥2 times/wk	0.57 [0.28–1.15] high 0.71 [0.50–1.01] medium	Age, visit year, age at menarche, family history, parity, age at first full-term pregnancy, drinking, intake of fruit, dietary restriction, history of stomach cancer screening and occupation.
kruk et al 2003	Study on breast cancer risk conducted between October 1997 and October 1998 in Stettin province. *257/565*	Self-administered questionnaire	Breast cancer	<u>BMI</u> lean ≤ 24 kg/m2 Large > 24 kg/m2 <u>OPA MET</u> sedentary <2 light 2-3 medium >3	BMI large vs OPA Sedentary 1 (ref) Light 0.46 (0.2–1.07) Medium 0.70 (0.32–1.53)	Stress experience.
Maleki et al 2020	Not clearly stated. Hospital-based case–control study (Imam Khomeini Hospital Complex in the capital city of Tehran). Cases were recruited from September 2011 to May 2016. *958/967*	Trained interviewers	Breast Cancer	<u>BMI</u> 18.5–24.9, 25–29.9, ≥ 30 <u>PA</u> Active >-25MET Moderate 10-25 MET Inactive <10 MET	BMI vs moderate levels of physical (OR = 0.75; 95%CI: 0.61, 0.93) BMI vs high levels of physical activity (OR = 0.50, 95%CI: 0.38, 0.65)	Age (continuous), age at menarche, education, body mass index (BMI), parity, breastfeeding (months), OCP usage (months), physical activity, and age at first childbirth.

Malin et al 2005	The Shanghai Breast Cancer Study. Permanent residents of urban Shanghai, enrolled in the study between August 1996 and March 1998. Women ages 25 to 64 who were newly diagnosed with breast cancer, and a random sample of healthy controls. *1459/1556, Population based registry.*	In-person interviews	Breast Cancer	<u>BMI</u> <21, <21 - <25 >25 PA comparison varied	Higher BMI vs exercised (OR, 0.75; 95% CI, 0.38-1.47)	Age at interview, education, income, history of fibroadenoma, history of breast cancer among first-degree relatives, and ever had live birth.
Maliniak et al 2020	American Cancer Society's (ACS) Cancer Prevention Study II (CPS-II) Nutrition Cohort. Postmenopausal women (mean age at baseline = 63.5 years). *NA*	Baseline self-reported (BMI and PA)	Breast, Endometrial, Colorectal cancer	<u>MVPA</u> 0 > 0– < 7.5 7.5– < 15 ≥ 15 <u>BMI</u> 18.5– < 25 25– < 30 ≥ 30 kg/m2	High BMI vs low PA (HR = 1.42, 95% CI: 1.22 − 1.67)	Age at baseline, race, education, smoking frequency and duration, alcohol intake, American Cancer Society diet score, and history of postmenopausal hormone therapy use; models for breast and endometrial cancer additionally adjusted for: age at menopause and parity/age at first birth (combined variable).

Maruti et al 2008	The Nurses' Health Study II (NHSII) 1989. *N=116,608*	self-administered questionnaire	Breast cancer	BMI ≤ 25 kg/m2 > 25 kg/m PA met-h/week < 21.0 21.0–29.9 30.0–38.9 39.0–53.9 ≥ 54.0	RR=0.68, 95% CI= 0.48 to 0.98	Age at menarche, regularity and length ofmenstrual cycle during youth and adulthood, and BMI
McCullough et al 2012	The Long Island Breast Cancer Study Project, case-control study; women of all ages (age range, 20-98 years) and races who were newly diagnosed with first primary in situ or invasive breast cancer between August 1, 1996, and July 31, 1997. *1504 cases (N = 233 in situ, N =1271 invasive) and 1555 controls; N.A*	Trained interviewers	Breast cancer	<u>Recreational PA</u> No RPA Low RPA High (RPA) <u>BMI</u> <18.5 18.5-24.99 25.0-29.99 ≥30.0	Overall, no joint association	Age-Adjusted

Neil-Sztramko et al 2017	Systematic review. *29 papers: 18 cohort and 11 case–control studies.*	Varied	Breast Cancer	Varied	High vs low levels of physical activity for women with a BMI<25 kg/m2 (RR 0.85, 95% CI 0.79, 0.92) ≥25 kg/m2 (RR 0.87, 95% CI 0.81, 0.93) ≥30 kg/m2 (RR: 0.93, 95% CI 0.76, 1.13)	
Pan et al 2008	The National Enhanced Cancer Surveillance System. *810/3106*	Self-reported: Questionnaire	Kidney cancer	BMI= WHO classification <u>PA</u> (MET-hour/wk) <6.3 6.3 to <17.0 17.0 to <34.4 >-34.4	No significant effect modification of total physical activity on obesity	Age, province, education, total energy intake, vegetable intake, smoking pack-years, and self-reported exposure to pesticides, herbicides, vinyl chloride, benzidine, benzene, mineral or cutting oil, and dyestuffs.
Patel et al 2008	American Cancer Society Cancer Prevention Study II Nutrition Cohort. Postmenopausal women (aged 50-74) with intact uteri who were cancer-free at enrollment. *466 cases (N=42,672)*	Self-reported Baseline and follow up questionnaire	Endometrial cancer	Baseline recreational activity MET-hr/week None 0<–<7 7–<17.5 17.5–<31.5 31.51+ <u>BMI</u> (<25.0 25.0–<27.5 27.5–<30.0 ≥30.0)	BMI significantly modified the association between physical activity and endometrial cancer risk	Age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and post-menopausal HT use.

Peters et al 2009	NIH-AARP Diet and Health Study. *182,862 (6609 cases)*	Self-administered questionnaire	Breast cancer	BMI (kg/m2) ≥25.0 <25.0 PA(times per week) Inactive <1 1–2 3–4 ≥5	PA vs BMI ≥25.0 1.0 (Ref) OR (0.98, 0.89–1.08) OR (0.98, 0.90–1.08) OR (0.92, 0.84–1.01) OR (0.86, 0.77–0.96)	Education level , smoking status, family history of breast cancer, menopausal hormone use, age at first birth , age at menarche, age at menopause, parity , and alcohol intake
Ratnasinghe et al 2010	Global Epidemiology Study *1463/4862*	Self-administered questionnaire		BMI Healthy Weight Over Weight Obese PA <30 30–150 ≥150	BMI vs PA 30–150 and ≥150 OR (0.47, 0.40, 0.54) OR (0.62, 0.54, 0.72)	Age, race, smoking
Shin et al 2008	Shanghai Breast Cancer Study, women age 20-64 (phase I), 20-70 (phase II). *3458/3474*	Trained interviewers	Breast cancer	<u>BMI</u> <20.9 (Q1) 21–24.9 (Q2) ≥25 (Q3) <u>TPA</u> ≥20.5 10.9–20.4 <10.8	Q3 vs <10.8 OR (2.6, 1.5–4.7)	Adjusted for age (3-years interval), study phase, education, menopausal status.

Silvera et al 2006	National Breast Screening Study. A randomized controlled trial of screening for breast cancer. A total of 89,835 women aged 40–59 years with no history of breast cancer were recruited into the trial between 1980 and 1985. *1673 cases (N= 40,318)*	Self-administered questionnaire	Breast cancer	BMI < 25 25– < 29 ≥ 30 kg/m2 <u>VPA</u> none Any <u>VPA</u> 0-30 30-60 > 60	BMI ≥ 30 kg/m2 vs PA none OR (1.29, 0.78–2.14)	Age, alcohol, smoking history, use of oral contraceptives, use of hormone replacement therapy, parity, age at menarche , age at first live birth, family history of breast cancer, history of breast disease, menopausal status at baseline, study center, and randomization group.