Mobile Phone Use and Risks of Overall and 25 Site-Specific Cancers: A Prospective Study from the UK Biobank Study

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ABSTRACT

Background: The association between mobile phone use and incident cancers remains uncertain. We aimed to investigate the relationships of mobile phone use with incident overall and 25 site-specific cancers in men and women.

Methods: A total of 431,861 participants ages 38 to 73 years without prior cancers were included from the UK Biobank. Of these, 46.7% were male. Participants who used a mobile phone at least once per week to make or receive calls were defined as mobile phone users. The study outcomes were incident overall and 25 site-specific cancers.

Results: During a median follow-up of 10.7 years, 35,401 (17.5%) men and 30,865 (13.4%) women developed overall cancer. Mobile phone use was significantly associated with higher risks of incident overall cancer [HR, 1.09; 95% confidence interval (CI): 1.06–1.12], nonmelanoma skin cancer (NMSC; HR, 1.08; 95% CI: 1.03–1.14), urinary tract cancer (HR, 1.18; 95% CI:1.05–1.32), and prostate cancer (HR, 1.19; 95% CI: 1.13–1.25) in men, and incident overall cancer (HR, 1.03; 95% CI: 1.00–1.06), NMSC (HR, 1.07; 95% CI: 1.01–1.13), and vulva cancer (HR, 1.74; 95% CI: 1.00–3.02) in women, but not with other cancers. Among mobile phone users, there was a dose–response relationship of length of mobile phone use with incident NMSC in men and women, and prostate cancer in men (all $P_{trend} < 0.05$).

Conclusions: There was a dose–response relationship of length of mobile phone use with incident NMSC in men and women, and prostate cancer in men.

Impact: Our findings underscore the importance of limiting mobile phone use or keeping a distance from mobile phone for primary prevention of NMSC and prostate cancer.

Introduction

In recent years, mobile phones have become daily devices for most people, and the number of global mobile phone subscriptions has reached about 8.65 billion in 2021 (1). Although mobile phones facilitate people's daily lives, concerns have arisen over the potential health risks, such as the carcinogenic risks, of radiofrequency electromagnetic fields (RF-EMF) emitted from mobile phones. In 2011, RF-EMFs were classified as possible carcinogen to humans (Group 2B) by the International Agency for Research on Cancer, based on limited evidence of an increased risk of glioma among heavy users of mobile phones (2). For example, three recent case–control studies, including the CERENAT case–control study (3), the INTERPHONE international case–control study (4) and a recent case–control study by Hardell and colleagues (5), found that heavy mobile phone use was associated with increased risk of brain tumors. However, case–control studies cannot determine the temporal relationship between mobile phone use and cancer incidence.

To date, two previous prospective studies have investigated the association between mobile phone use and the risk of cancer. However, both studies have significant limitations that make it difficult to draw accurate conclusions. A cohort study in Denmark found that there was no significant association of mobile phone use with brain tumors (6), acoustic neuromas (7), skin cancers (8), salivary gland tumors, eye tumors, leukemias, breast cancers, or prostate cancers (9). However, there was a significant decrease in the risks of overall cancer and smoking-related cancers (mainly driven by lung, oral/pharyngeal, esophageal, liver, and pancreatic cancers) in men, and a significant increase in the risk of smoking-related cancers (mainly driven by cervical and kidney cancers) in women (9). Limitations of this study included the possible exposure misclassification caused by the use of subscription information rather than mobile phone use, lack of data on the amount of mobile phone use, and lack of consideration of any confounding factors. Another cohort study, the UK Million Women Study, showed that mobile phone use was not associated with increased incidence of all intracranial central nervous system (CNS) tumors, glioma, meningioma, pituitary tumors or non-CNS cancers (10, 11). However, this study included only middle-aged women, and did not take into account many important confounding factors, including diet, family history of cancers, menopause status, age at menarche, and oral contraceptive pill use, etc. As such, to date, the prospective relationships of mobile phone use with risks of site-specific cancers remain uncertain.

To address the above knowledge gaps, we aimed to estimate the associations between mobile phone use and the risk of incident overall and 25 site-specific cancers in general population, using data from the UK Biobank.

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Materials and Methods

Data source and study population

The UK Biobank is a large-scale, population-based cohort study, with more than 0.5 million participants ages 37 to 73 years recruited in 2006 to 2010. Participants were enrolled from 22 assessment centers across England, Scotland, and Wales, where they provided information on demographic, lifestyle and other health-related characteristics through self-administered, touchscreen questionnaires, face-to-face interviews, and a series of physical measurements, as well as provided biological samples for laboratory analyses. More details of UK Biobank design and data collection have been described previously (12, 13). The UK Biobank was approved by the North West Research Ethics Committee (11/NW/0382). All participants signed a written informed consent to the study at the time of enrollment. This study was conducted in accordance with the Declaration of Helsinki. Participants were followed for the development of incident diagnoses through linkage to their health-related records and follow-up study visits.

In the current analyses, participants who were diagnosed with any cancer or whose cancer status was unknown at baseline ($n = 52{,}202$), and participants with missing values in the mobile phone use behavior questionnaires ($n = 18{,}351$) were excluded. The final study population included the remaining 431,861 participants (Supplementary Fig. S1).

Measurements of mobile phone use behaviors

Data on behaviors of mobile phone use (length of mobile phone use, weekly usage of mobile phone, hands-free device/speakerphone use with mobile phone, and usual side of head for mobile phone use) were collected through self-administered, touchscreen questionnaires designed by UK Biobank at the initial assessment visit (2006–2010; https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/TouchscreenQuestionsMainFinal.pdf). Length of mobile phone use was obtained based on the following question, "For approximately how many years have you been using a mobile phone at least once per week to make or receive calls?", and five valid options were given to select: "Never used mobile phone at least once per week", "One year or less", "Two to 4 years", "Five to 8 years", and "More than 8 years". Participants who used a mobile phone at least once per week to make or receive calls were defined as mobile phone users (14–16).

Among mobile phone users, questions on weekly usage of mobile phone, hands-free device/speakerphone use with mobile phone, and usual side of head for mobile phone use, were further asked. Weekly usage of mobile phone was evaluated on the basis of the following question, "Over the last 3 months, on average how much time per week did you spend making or receiving calls on a mobile phone?", and six valid options were given to select: "Less than 5 minutes", "5–29 minutes", "30–59 minutes", "1–3 hours", "4–6 hours", and "More than 6 hours". Hands-free device/speakerphone use with mobile phone was assessed on the basis of the following question, "Over the last 3 months, how often have you used a hands-free device/speakerphone when making or receiving calls on your mobile?", and five valid options were given to select: "Never or almost never", "Less than half the time", "About half the time", "More than half the time", and "Always or almost always". Usual side of head for mobile phone use was obtained on the basis of the following question: "On what side of the head do you usually use a mobile phone?", and three valid options were given to select: "Left", "Right", and "Equally left and right".

Measurements of covariates

Detailed information on covariates were obtained from touchscreen questionnaires and face-to-face interviews at baseline, including age, sex, race, Townsend deprivation score (TDI), educational levels, smoking status, alcohol drinking, physical activity, prevalent morbidity (including hypertension, diabetes, hypercholesteremia, depression, stroke, myocardial infarction, and angina), family history of cancer, use of NSAIDs, use of dietary supplements, sun exposure factors (including skin color, skin reaction to sun exposure, hair color, sun or UV protection use, and solarium use), and female-specific factors (including menopause status, age at menarche, number of live births, oral contraceptive pill use, and hormone replacement therapy use). Women were defined as being postmenopausal if they reported that their periods had stopped; or reported a history of bilateral oophorectomy; or ages 55 years or older for those with unknown self-reported menopausal status (17). Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

A healthy diet score was calculated using a more recent dietary recommendation for cardiovascular health, which considered adequate intake of fruits, vegetables, whole grains, fish, shellfish, dairy products, and vegetable oils, and reduced or no intake of refined grains, processed meats, unprocessed meats, and sugar-sweetened beverages (18). Time spent on sedentary behaviors included watching television, driving, and leisure-time computer use. Total mental health complaints were calculated by adding up answers to 13 mental health questions on mood swings, miserableness, irritability, sensitivity/hurt feelings, fed-up feelings, nervous feelings, worrier/anxious feelings, tense/highly strung, worry too long after embarrassment, suffer from nerves, loneliness/isolation, guilty feelings, and risk taking (19). Further details of covariates measurements can be found in the UK Biobank online protocol (http://www.ukbiobank.ac.uk).

Study outcomes

The outcomes for this study were incidences of overall cancer and 25 most common site-specific cancers (with at least 100 cases in women, and 100 cases for men only cancers, for consistency across sexes). Incident cancer was defined as the first record of cancer, at hospitalization, cancer register, or death register.

The International Classification of Diseases, 10th revision (ICD-10) was used to define overall cancer (C00-C97), and the following 25 site-specific cancers: head and neck (C00-C14, C30-C32), esophagus (C15), stomach (C16), small intestine (C17), colorectum (C18-C20), anus and anal canal (C21), liver (C22), pancreas (C25), lung (C33, C34), melanoma (C43), nonmelanoma skin cancer (NMSC; C44), mesothelial and soft tissue (C45-C49), breast (C50), vulva (C51), cervix (C53), uterus (C54, C55), ovary (C56), prostate (C61), kidney (C64), urinary tract (C65-C67), brain/CNS/ intracranial (C70-C72), thyroid gland (C73), non–Hodgkin lymphoma (C82-C86), multiple myeloma (C90), and leukemia (C91-C95). Of these, 19 cancer sites were estimated for both men and women, one were specific to men (prostate) and five to women (breast, vulva, cervix, uterus, and ovary). The diagnosis of glioma, a histologic subtype of brain/CNS/intracranial tumors, was established according to the ICD for Oncology, third edition codes (ICD-O-3: 9380-9480), provided by the cancer registry.

Statistical analyses

Baseline characteristics were described as mean ± SD or median [interquartile range (IQR)] for continuous variables and percentages for categorical variables. Comparisons of characteristics according to the incident cancer status (yes vs. no) were conducted by χ^2 tests for categorical variables and t tests for continuous variables among men and women, respectively.

Cox proportional hazards models [HRs and 95% confidence intervals (CI)] were used to estimate the association between mobile phone use (users vs. non-users) and the risk of overall and site-specific

cancers. We performed the minimally adjusted model by adjusting for age. Model 1 was adjusted for age (continuous), Townsend deprivation index (continuous), race (White and non-White), educational level (college or university degree, no college or university degree, and missing), BMI (continuous), smoking status (never, previous, and current), alcohol drinking (never, <1 time/week, 1–4 times/ week, and daily or almost daily), healthy diet scores (continuous), physical activity (≤4 days/week and >4 days/week moderate/vigorous physical activity, and missing), sedentary behavior (continuous), total mental health complaints (continuous), prevalence of diseases (hypertension, diabetes, hypercholesteremia, depression, stroke, heart attack/myocardial infarction, angina; no and yes), family history of cancer (no and yes), use of NSAIDs (no, yes, and missing), and use of dietary supplements (no and yes); and for women only: menopause status (no, yes, and missing), age at menarche (<12, 12–<14, and ≥14 years, and missing), number of live births (continuous), use of oral contraceptive pill (no and yes), and hormone replacement therapy (no and yes). In analyses on skin cancer (including NMSC and melanoma), model 1 was further adjusted for skin color (very fair, fair, light olive, dark olive, black/brown, and missing), skin reaction to sun exposure (never tan, only burn, get mildly or occasionally tanned, get moderately tanned, get very tanned, and missing), hair color (blonde, light brown, red, dark brown, black, and other), sun or UV protection use (do not go out in sunshine, always, most of the time, sometimes, and never/ rarely), and solarium use (<1, 1–2, ≥3 times/year, and missing). Stratified analyses were conducted by age groups (≤50, 51–60, ≥61 years). For the analysis on vulva cancer in women, we combined the age group ≤50 years with the age group 51–60 years, because among mobile phone non-users, no cases were found in the age group ≤50 years. The likelihood ratio test was used to examine the significance of the interaction. In addition, we limited our analysis of brain/CNS/intracranial tumors to gliomas to examine the potential effect of mobile phone use on the risk of gliomas.

Among mobile phone users, we further examined the relationship of mobile phone use behaviors, including length of mobile phone use, weekly usage time of mobile phone, hands-free device/speakerphone use with mobile phone, and usual side of head for mobile phone use, with the risk of incident cancers, which were significantly associated with mobile phone use and estimated the potentially linear trend. The linear trend test was conducted by treating categories of length of mobile phone use, weekly usage time of mobile phone, and hands-free device/speakerphone use with mobile phone as numeric variables. In analyses of behaviors of mobile phone use among mobile phone users, these behaviors were further mutually adjusted in the model 2.

Furthermore, several sensitivity analyses were conducted to test the robustness of the results. First, we further adjusted for the year of enrollment. Second, we excluded the cases reported during the first 2 years of follow-up to minimize reverse causality. Third, we excluded the cases reported before October 1, 2012 (2 years after the latest enrollment date). Fourth, length of mobile phone use was treated as a time-dependent variable. The given categories of length of mobile phone use were transformed to numeric variables, by encoding groups of "≤ 1 year", "2–4 years", "5–8 years", and ">8 years" as 0.5, 3, 6.5, and 9 years, respectively. We assume that mobile phone use continued and that for every additional year of follow-up, the number of years of mobile phone use would increase by 1 year. For each covariate, answers of "do not know" or "prefer not to answer" were treated as missing data. When the missing rate is <1%, we combined the missing data with the reference group for categorical variables, or coded the missing data as median values for continuous variables. When the missing rate is ≥1%, an "unknown/ missing" category was created.

In all analyses, a two-tailed $P < 0.05$ was considered to be statistically significant. Analyses were conducted using R software (version 4.1.1, http://www.R-project.org/) with the R package survival for Cox proportional hazards regression and *epiDisplay* for likelihood ratio test.

Data availability

The UK Biobank data are available on application to the UK Biobank.

Results

Baseline characteristics of the participants

As demonstrated in the flow chart (Supplementary Fig. S1), a total of 431,861 participants were included in the current study. Of these, 367,033 (85.0%) participants were mobile phone users. The mean (SD) age was 56.2 (8.1) years, and 201,868 (46.7%) were male.

Baseline characteristics of study participants were summarized in **Table 1**; Supplementary Tables S1 and S2. Participants who developed cancer were older, more likely to be White, current smokers; had higher prevalence of hypertension, diabetes, hypercholesteremia, family history of cancer, lower TDI, education levels, and higher frequency of alcohol consumption in both men and women. Moreover, women who developed cancer were more likely to be postmenopausal, and to use hormone replacement therapy, and less likely to use oral contraceptive pill (**Table 1**; Supplementary Table S1). Compared with mobile phone non-users, mobile phone users were younger, more likely to be current smokers, get tanned, and use sun or UV protection, less likely to be White, and had higher BMI, frequency of alcohol consumption, sedentary time, frequency of solarium use, and darker skin color (Supplementary Table S2). In cancer and non-cancer cases, participants with older age had a lower proportion of mobile phone use (Supplementary Table S3).

Associations of mobile phone use with incident overall and site-specific cancers

During a median follow-up of 10.7 (25th–75th, 9.8–11.5) years, a total of 35,401 (17.5%) men and 30,865 (13.4%) women developed overall cancer.

In men, compared with mobile phone non-users, a significantly higher risk of incident overall cancer (HR, 1.09; 95% CI: 1.06–1.12), NMSC (HR, 1.08; 95% CI: 1.03–1.14), urinary tract cancer (HR, 1.18; 95% CI: 1.05–1.32), and prostate cancer (HR, 1.19; 95% CI: 1.13–1.25) was found among mobile phone users (**Fig. 1**; Supplementary Tables S4 and S5). There was no significant association of mobile phone use with incident cancers of other sites (**Fig. 1**; Supplementary Table S4) and gliomas (Supplementary Table S6).

In women, compared with mobile phone non-users, a higher risk of incident overall cancer (HR, 1.03; 95% CI: 1.00–1.06), NMSC (HR, 1.07; 95% CI: 1.01–1.13), and vulva cancer (HR, 1.74; 95% CI: 1.00–3.02) was found among mobile phone users (**Fig. 2**; Supplementary Tables S7 and S8). No significant association was found between mobile phone use and incident cancers of other sites and gliomas (Supplementary Table S6).

Age did not significantly modify the association of mobile phone use with the risk of overall cancer, NMSC, prostate cancer and urinary tract cancer in men, and overall cancer, NMSC and vulva cancer in women (all $P_{interaction} > 0.05$; Supplementary Fig. S2 and S3).

In sensitivity analyses, further adjusting for the year of enrollment (Supplementary Fig. S4), excluding the first 2 years of cases (Supplementary Fig. S5 and S6) or cases before October 1, 2012

Table 1. Baseline characteristics of study participants by cancer status in men and women.

Baseline characteristics	Female ($N = 229,993$)		Male ($N = 201,868$)	
	No cancer	Incident cancer	No cancer	Incident cancer
Number of participants	199,128	30,865	166,467	35,401
Mobile phone users, *n* (%)	170,744 (85.7)	25,507 (82.6)	142,138 (85.4)	28,644 (80.9)
Age, years, mean (SD)	55.5 (8.0)	58.8 (7.4)	55.5 (8.2)	60.7 (6.5)
White, *n* (%)	187,406 (94.4)	29,929 (97.2)	156,183 (94.2)	34,339 (97.4)
Townsend deprivation index, mean (SD)	−1.4 (3.0)	−1.5 (3.0)	−1.3 (3.1)	−1.5 (3.1)
College or University degree, *n* (%)	64,411 (32.7)	8,971 (29.4)	58,466 (35.5)	10,926 (31.3)
BMI, kg/m^2, mean (SD)	27.0 (5.2)	27.3 (5.2)	27.8 (4.3)	27.9 (4.2)
Current smoker, *n* (%)	17,081 (8.6)	3,052 (9.9)	20,563 (12.4)	4,610 (13.1)
Daily or almost daily alcohol consumption, *n* (%)	31,632 (15.9)	5,472 (17.7)	41,189 (24.8)	10,122 (28.6)
Healthy diet score, median (IQR)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)	3.0 (2.0,4.0)
Moderate/ vigorous physical activity, *n* (%)				
≤4 days/week	111,143 (59.8)	17,109 (59.9)	91,790 (57.6)	19,230 (57.2)
>4 days/week	74,820 (40.2)	11,444 (40.1)	67,630 (42.4)	14,394 (42.8)
Sedentary time, hours, mean (SD)	4.4 (2.2)	4.4 (2.1)	5.3 (2.7)	5.3 (2.6)
Total mental health complaints, median (IQR)	4.0 (2.0,7.0)	4.0 (2.0,7.0)	3.0 (1.0,6.0)	3.0 (1.0,6.0)
Use of NSAIDs, *n* (%)	82,184 (41.7)	12,707 (41.6)	61,430 (37.4)	14,311 (41.0)
Use of dietary supplement, *n* (%)	109,287 (55.1)	17,780 (57.8)	72,199 (43.6)	17,280 (49.1)
Family history of cancer	68,167 (34.2)	12,018 (38.9)	55,166 (33.1)	13,607 (38.4)
Women's health				
Postmenopausal status, *n* (%)	134,164 (71.5)	24,868 (83.8)	—	—
Age at menarche, *n* (%)			—	—
<12 years	38,338 (19.8)	6,125 (20.4)	—	—
12–<14 years	84,338 (43.6)	12,992 (43.3)	—	—
≥14 years	70,740 (36.6)	10,875 (36.3)	—	—
Number of live births, median (IQR)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	—	—
Oral contraceptive pill use, *n* (%)	163,278 (82.2)	24,265 (78.8)	—	—
Hormone replacement therapy use, *n* (%)	71,325 (35.9)	14,040 (45.6)	—	—
Length of mobile phone use among mobile phone users, *n* (%)				
≤1 years	5,810 (3.4)	933 (3.7)	3,650 (2.6)	903 (3.2)
2–4 years	41,466 (24.3)	6,492 (25.5)	21,941 (15.4)	4,972 (17.4)
5–8 years	67,450 (39.5)	10,396 (40.8)	45,591 (32.1)	9,229 (32.2)
>8 years	56,018 (32.8)	7,686 (30.1)	70,956 (49.9)	13,540 (47.3)

Abbreviations: BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs.

(Supplementary Fig. S7 and S8), did not substantially change the results in men or women.

Association of mobile phone use behaviors with incident cancers, which were significantly associated with mobile phone use

Among mobile phone users, there was a significantly positive dose–response relationship of length of mobile phone use (≤1, 2–4, 5–8, and >8 years) with incident overall cancer in both men ($P_{trend} < 0.001$) and women ($P_{trend} = 0.025$), incident NMSC in both men ($P_{trend} < 0.001$) and women ($P_{trend} = 0.004$), and prostate cancer ($P_{trend} < 0.001$) in men (**Table 2**), but not with urinary tract cancer in men and vulva cancer in women (**Table 2**). There was only a slight difference in follow-up time among different groups of length of mobile phone use (all differences <0.5 year; Supplementary Table S9), so the groups classified by length of mobile phone use based on baseline assessments should not have changed substantially during follow-up. In addition, treating length of mobile phone use as a time-dependent variable did not significantly change the results (Supplementary Table S10).

Moreover, weekly usage of mobile phone, hands-free device/-speakerphone use and usual side of head for mobile phone use were not significantly associated with incident overall cancer, NMSC in men and women, prostate cancer and urinary tract cancer in men, and vulva cancer in women (Supplementary Tables S11 and S12), except a higher risk of incident NMSC among those who used a mobile phone usually on the right head (vs. equally left and right head; HR, 1.10; 95% CI: 1.01–1.20) in men (Supplementary Table S11).

Discussion

In this large-scale, population-based cohort study, we first observed that mobile phone use was prospectively associated with a higher risk of incident overall cancer, NMSC, urinary tract cancer, and prostate cancer in men, and overall cancer, NMSC and vulva cancer in women. Moreover, among mobile phone users, length of mobile phone use was significantly correlated with incident NMSC in both men and women, and prostate cancer in men, following a dose–response relationship.

Consistent with the two previous cohort studies (6–11, 20), the current study also found that there was no significant association of mobile phone use with cancers of brain/CNS/intracranial, melanoma, thyroid gland, head and neck, stomach, colorectum, leukemia, and non–Hodgkin lymphoma in men and women; and multiple myeloma, urinary tract cancer, uterus cancer, ovary cancer, and breast cancer in women. Of note, although the Danish cohort study (9) found that mobile phone use was related to a decreased risk of smoking-related cancers in men, and an increased risk of smoking-related cancers in women, and the UK Million Women Study (10) found a reduced risk among mobile phone users (vs. non-users) for lung cancer in women,

Cancer site/cancer (ICD 10 code)	Non-users Total/cases	Users Total/cases	Users vs. Non-users HR (95% CI)
Overall cancer (C00 - C97)	31,086/6,757	170,782/28,644	1.09(1.06–1.12)
Anus and anal canal (C21)	31,086/18	170,782/72	0.90(0.52–1.53)
Lung (C33, C34)	31,086/510	170,782/1,735	0.93(0.84–1.03)
Multiple myeloma (C90)	31,086/131	170,782/448	0.93(0.76–1.14)
Liver (C22)	31,086/116	170,782/418	0.95(0.76–1.18)
Colorectum (C18-C20)	31,086/700	170,782/2,679	0.96(0.88–1.05)
Stomach (C16)	31,086/145	170,782/551	0.97(0.80–1.18)
Mesothelial and soft tissue (C45-C49)	31,086/141	170,782/513	0.98(0.81–1.20)
Brain/CNS/Intracranial (C70-C72)	31,086/101	170,782/423	1.01(0.80–1.27)
Non-Hodgkin lymphoma (C82-C86)	31,086/246	170,782/988	1.03(0.89–1.19)
Melanoma (C43)†	31,086/268	170,782/1,219	1.05(0.92–1.21)
Kidney (C64)	31,086/194	170,782/848	1.06(0.90–1.25)
Nonmelanoma skin cancer (C44)†	31,086/2,242	170,782/9,344	1.08(1.03–1.14)
Pancreas (C25)	31,086/162	170,782/642	1.08(0.91–1.30)
Head and neck (C00-C14, C30-C32)	31,086/149	170,782/781	1.11(0.92–1.33)
Oesophagus (C15)	31,086/174	170,782/753	1.13(0.95–1.35)
Leukaemia (C91-C95)	31,086/173	170,782/729	1.15(0.96–1.37)
Small intestine (C17)	31,086/32	170,782/151	1.15(0.77–1.71)
Urinary tract (C65-C67)	31,086/389	170,782/1,661	1.18(1.05–1.32)
Prostate (C61)	31,086/1,974	170,782/8,651	1.19(1.13–1.25)
Thyroid gland (C73)	31,086/17	170,782/98	1.26(0.73–2.17)

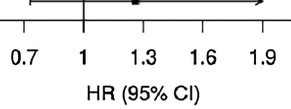

Figure 1.

Association of mobile phone use status (users vs. non-users) with incident site-specific cancers in men*. *Adjusted for age, Townsend deprivation index, race, educational level, BMI, smoking status, alcohol drinking, healthy diet scores, physical activity, sedentary behavior, total mental health complaints, prevalent of disease (hypertension, diabetes, hypercholesteremia, depression, stroke, myocardial infarction, angina), family history of cancer, medicine use of NSAIDs, use of dietary supplement. †Additionally adjusted for skin color, skin reaction to sun exposure, hair color, sun or UV protection use, and solarium use.

the Danish cohort study did not have detailed information about the use of mobile phones and the related confounding factors, and the UK Million Women Study also did not take into account many important confounding factors. As such, the two studies concluded that residual confounding and chance might contribute to these significant associations. Our current study, with detailed information of mobile phone use, and comprehensive adjustments of a series of confounding factors, did not find significant relationships of mobile phone use with these cancers.

However, we first found that there was a significant dose–response association of length of mobile phone use with a higher risk of incident NMSC in men and women, and prostate cancer in men, while the Danish cohort study found no significant relationship of mobile phone use with incident NMSC and prostate cancer (8, 9). The difference between our results and those of the previous cohort study may be due to the possible misclassification of exposure and a lack of consideration of confounding factors in the Danish cohort. In addition, we found that among men, those who usually used mobile phones on the right head (vs. equally on the left and right head) had a higher risk of incident NMSC. This seems unexplainable because no such increase was found among women, so this finding among men might be a role of chance.

Moreover, to date, the relationship of mobile phone use with cancers of mesothelial and soft tissue, small intestine, anus and anal canal in men and women, multiple myeloma in men, and vulva cancer in women has not been reported in previous prospective studies. Of these cancer types, the current study first demonstrated a significant association of mobile phone use with a higher risk of vulvar cancer in women, but not with any other cancers. However, there was no significant dose–response relationship between length of mobile phone use and risk of vulvar cancer. As such, the mobile phone use and vulvar cancer association remains to be further investigated.

Findings of the current study imply a possible causal relationship of mobile phone use with incident NMSC and prostate cancer: (i) Dose–response relationship of anatomic distance: skin is the first organ to be exposed to RF-EMF. When carrying a mobile phone on the belt or in a pants pocket, it is closer to the prostate. Previous studies have shown that the distance of the source of RF-EMF from the tissue or organ is one of the determinants of corresponding specific absorption

Cancer site/cancer (ICD 10 code)	Non-users Total/cases	Users Total/cases	Users vs. Non-users HR (95% CI)
Overall cancer (C00 - C97)	33,742/5,358	196,251/25,507	1.03(1.00–1.06)
Uterus (C54, C55)	33,742/321	196,251/1,213	0.91(0.80–1.04)
Thyroid gland (C73)	33,742/51	196,251/267	0.91(0.67–1.25)
Oesophagus (C15)	33,742/69	196,251/244	0.92(0.70–1.22)
Brain/CNS/Intracranial (C70-C72)	33,742/77	196,251/316	0.92(0.71–1.20)
Urinary tract (C65-C67)	33,742/138	196,251/533	0.94(0.77–1.14)
Colorectum (C18-C20)	33,742/512	196,251/2,066	0.95(0.86–1.05)
Kidney (C64)	33,742/103	196,251/458	0.98(0.78–1.23)
Leukaemia (C91-C95)	33,742/113	196,251/480	0.99(0.80–1.23)
Ovary (C56)	33,742/224	196,251/999	1.01(0.87–1.17)
Cervix (C53)	33,742/26	196,251/129	1.02(0.65–1.60)
Non-Hodgkin lymphoma (C82-C86)	33,742/195	196,251/848	1.03(0.88–1.22)
Lung (C33, C34)	33,742/367	196,251/1,601	1.04(0.93–1.18)
Breast (C50)	33,742/1,369	196,251/7,493	1.05(0.99–1.12)
Multiple myeloma (C90)	33,742/73	196,251/339	1.06(0.82–1.38)
Nonmelanoma skin cancer (C44)†	33,742/1,642	196,251/7,822	1.07(1.01–1.13)
Melanoma (C43)†	33,742/215	196,251/1,199	1.13(0.97–1.32)
Mesothelial and soft tissue (C45-C49)	33,742/85	196,251/398	1.16(0.90–1.48)
Stomach (C16)	33,742/50	196,251/237	1.19(0.86–1.63)
Pancreas (C25)	33,742/111	196,251/516	1.20(0.96–1.50)
Liver (C22)	33,742/54	196,251/267	1.22(0.90–1.66)
Head and neck (C00-C14, C30-C32)	33,742/64	196,251/368	1.23(0.93–1.63)
Anus and anal canal (C21)	33,742/24	196,251/134	1.25(0.79–2.00)
Small intestine (C17)	33,742/17	196,251/134	1.66(0.98–2.82)
Vulva (C51)	33,742/17	196,251/107	1.74(1.00–3.02)

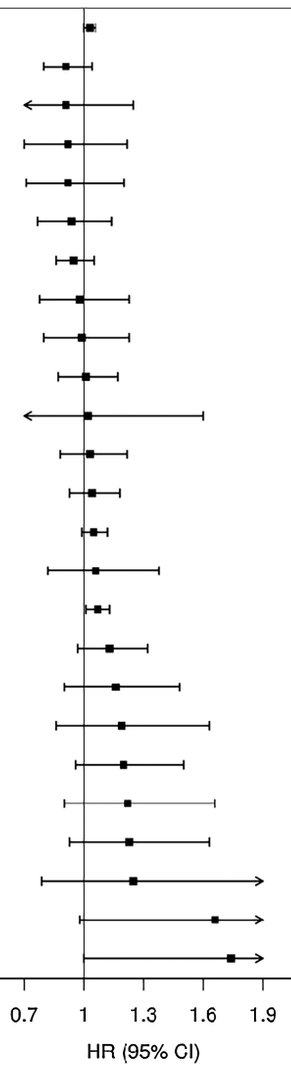

Figure 2.

Association of mobile phone use status (users vs. non-users) with incident site-specific cancers in women*. *Adjusted for age, Townsend deprivation index, race, educational levels, BMI, smoking status, alcohol drinking, healthy diet scores, physical activity, sedentary behavior, total mental health complaints, prevalent of disease (hypertension, diabetes, hypercholesteremia, depression, stroke, myocardial infarction, angina), family history of cancer, medicine use of NSAIDs, use of dietary supplement, menopause status, age at menarche, number of live births, oral contraceptive pill use, and hormone replacement therapy use. †Additionally adjusted for skin color, skin reaction to sun exposure, hair color, sun or UV protection use, and solarium use.

rate (21, 22), and thus the relatively close distance of skin and prostate with mobile phones may partly explain the observed increase risks of NMSC and prostate cancer; (ii) Temporal relationship: there was a significant association of mobile phone use at baseline with the risks of NMSC and prostate cancer during the 10.7 years of follow-up; (iii) Dose–response relationship of exposure time: among mobile phone users, there was a significantly positive dose–response relationship of length of mobile phone use with incident NMSC and prostate cancer. In addition, we found that length of mobile phone use, rather than weekly usage of mobile phone, was associated with incident cancers, suggesting that long-term exposure to RF-EMF might be more important in terms of the risk of incident cancers than short-term, high-dose exposure to RF-EMF from making or receiving calls. However, more studies are needed to further confirm our results and elucidate the underlying biological mechanisms.

Our study has several strengths, including a large sample size, a prospective design, comprehensive adjustments of confounding factors, and available information on site-specific cancers and various behaviors of mobile phone use. However, the current study also has several limitations. First, the current study was based on baseline information on mobile phone use. Because of the increasing number of mobile phone users over the years, mobile phone non-users at enrollment may use mobile phones in later years, thereby diluting the relationship of mobile phone use with the risk

Table 2. Among mobile phone users, the association of length of mobile phone use with incident overall cancer and NMSC in men and women, prostate cancer and urinary tract cancer in men, and vulva cancer in women.

			Age-adjusted model		Model 1[a]		Model 2[b]	
Length of mobile phone use (years)	***N***	**Cases (%)**	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Male								
Overall cancer (C00-C97)								
≤1	4,553	903 (19.8)	Ref		Ref		Ref	
2–4	26,913	4,972 (18.5)	0.99 (0.92–1.06)	0.802	0.99 (0.92–1.06)	0.684	0.98 (0.92–1.06)	0.671
5–8	54,820	9,229 (16.8)	1.02 (0.96–1.10)	0.521	1.01 (0.94–1.08)	0.767	1.01 (0.94–1.08)	0.812
>8	84,496	13,540 (16.0)	1.08 (1.01–1.16)	0.024	1.07 (1.00–1.14)	0.069	1.06 (0.99–1.14)	0.091
P_{trend}			<0.001		<0.001		<0.001	
Nonmelanoma skin cancer (C44)[c]								
≤1	4,553	251 (5.5)	Ref		Ref		Ref	
2–4	26,913	1,573 (5.8)	1.15 (1.01–1.32)	0.037	1.13 (0.99–1.29)	0.076	1.13 (0.99–1.29)	0.068
5–8	54,820	3,043 (5.6)	1.24 (1.09–1.41)	0.001	1.18 (1.04–1.34)	0.012	1.18 (1.04–1.35)	0.012
>8	84,496	4,477 (5.3)	1.32 (1.16–1.50)	<0.001	1.25 (1.10–1.42)	0.001	1.23 (1.08–1.40)	0.002
P_{trend}			<0.001		<0.001		<0.001	
Prostate (C61)								
≤1	4,553	236 (5.2)	Ref		Ref		Ref	
2–4	26,913	1,500 (5.6)	1.18 (1.03–1.36)	0.017	1.18 (1.03–1.35)	0.018	1.17 (1.02–1.35)	0.023
5–8	54,820	2,789 (5.1)	1.24 (1.09–1.42)	0.001	1.23 (1.08–1.41)	0.002	1.22 (1.06–1.39)	0.004
>8	84,496	4,126 (4.9)	1.33 (1.17–1.52)	<0.001	1.33 (1.16–1.51)	<0.001	1.30 (1.14–1.49)	<0.001
P_{trend}			<0.001		<0.001		<0.001	
Urinary tract (C65-C67)								
≤1	4,553	72 (1.6)	Ref		Ref		Ref	
2–4	26,913	291 (1.1)	0.74 (0.57–0.96)	0.023	0.74 (0.57–0.96)	0.022	0.73 (0.57–0.95)	0.020
5–8	54,820	536 (1.0)	0.78 (0.61–1.00)	0.047	0.78 (0.61–1.00)	0.047	0.77 (0.60–0.99)	0.039
>8	84,496	762 (0.9)	0.82 (0.64–1.04)	0.106	0.81 (0.63–1.03)	0.082	0.80 (0.62–1.02)	0.073
P_{trend}			0.710		0.927		0.982	
Female								
Overall cancer (C00-C97)								
≤1	6,743	933 (13.8)	Ref		Ref		Ref	
2–4	47,958	6,492 (13.5)	1.03 (0.96–1.10)	0.453	1.02 (0.95–1.09)	0.598	1.02 (0.96–1.10)	0.491
5–8	77,846	10,396 (13.4)	1.08 (1.01–1.15)	0.030	1.06 (0.99–1.13)	0.111	1.06 (0.99–1.14)	0.073
>8	63,704	7,686 (12.1)	1.08 (1.01–1.16)	0.028	1.05 (0.98–1.13)	0.145	1.06 (0.99,1.13)	0.109
P_{trend}			0.001		0.028		0.025	
Nonmelanoma skin cancer (C44)[c]								
≤1	6,743	261 (3.9)	Ref		Ref		Ref	
2–4	47,958	1,969 (4.1)	1.14 (1.00–1.29)	0.051	1.08 (0.95–1.23)	0.223	1.10 (0.96–1.25)	0.163
5–8	77,846	3,302 (4.2)	1.26 (1.11–1.43)	<0.001	1.18 (1.04–1.34)	0.011	1.20 (1.05–1.36)	0.005
>8	63,704	2,290 (3.6)	1.21 (1.06–1.37)	0.004	1.15 (1.01–1.31)	0.029	1.17 (1.03–1.34)	0.016
P_{trend}			0.003		0.007		0.004	
Vulva (C51)								
≤1	6,743	6 (0.1)	Ref		Ref		Ref	
2–4	47,958	33 (0.1)	0.80 (0.33–1.91)	0.612	0.84 (0.35–2.01)	0.690	0.83 (0.34–1.99)	0.669
5–8	77,846	40 (0.1)	0.70 (0.29–1.64)	0.409	0.74 (0.31–1.75)	0.492	0.71 (0.30–1.71)	0.450
>8	63,704	28 (0.0)	0.69 (0.28–1.67)	0.406	0.73 (0.30–1.78)	0.485	0.68 (0.27–1.70)	0.412
P_{trend}			0.386		0.445		0.349	

[a]Model 1: Adjusted for age, Townsend deprivation index, race, educational level, BMI, smoking status, alcohol drinking, healthy diet scores, physical activity, sedentary behavior, total mental health complaints, prevalent of disease (hypertension, diabetes, hypercholesteremia, depression, stroke, myocardial infarction, angina), family history of cancer, medicine use of NSAIDs, use of dietary supplement; and in women only: menopause status, age at menarche, number of live births, oral contraceptive pill use, and hormone replacement therapy use.
[b]Model 2: Adjusted for covariates in model 1 plus weekly usage of mobile phone, hands-free device/speakerphone use, and usual side of head for mobile phone use.
[c]Additionally adjusted for skin color, skin reaction to sun exposure, hair color, sun or UV protection use, and solarium use in Model 1.

of incident cancers. However, we further restricted our analyses to baseline mobile phone users, who are generally less likely to change their mobile phone use, and found a positive dose–response relationship of length of mobile phone use with the risk of incident NMSC in men and women, and prostate cancer in men. Second, consistent with previous studies, the lack of information on other uses of mobile phones other than making or receiving calls may lead to underestimation of mobile phone exposure, thereby diluting the relationships between mobile phone use and incident cancers. Mobile phone use is involved in many activities of daily life, ranging from calling and text messaging, to Internet-surfing, e-mailing, watching videos, getting traffic directions or listening to music, and is more pronounced among younger generation. Therefore, it is necessary to gather more information on mobile phone use in future studies to confirm our findings and provide more evidence for the potential carcinogenicity of improper

mobile phone use. Third, the relatively limited observed exposure time may lead to a loss of the association between mobile phone use and some slowly growing cancers. Fourth, the current study is observational, although a range of possible confounders were adjusted in the analysis, residual confounding from unknown or unmeasured factors cannot be exclude. Fifth, the participants were mainly European descent and healthier than the UK general population (23), which may limit generalizability of the results to other populations. Future studies are needed to explore the interaction between different ethnic genetic backgrounds and mobile phone use for the risk of cancer.

In conclusion, the current study found that there was a positive dose-response relationship between length of mobile phone use and risk of incident NMSC in both men and women and prostate cancer in men. The potential association of mobile phone use with the risk of urinary tract cancer in men and vulva cancer in women needs to be further verified. If further confirmed, our findings underscore the importance of limiting mobile phone use or keeping a distance from mobile phone for primary prevention of NMSC and prostate cancer in the general population.

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Authors' Contributions

Y. Zhang: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft. **Y. Zhang:** Conceptualization, data curation, validation, investigation. **Z. Ye:** Data curation, validation, investigation. **S. Yang:** validation, investigation. **M. Liu:** Validation, investigation. **Q. Wu:** Validation, investigation. **C. Zhou:** Validation, investigation. **P. He:** Validation, investigation. **X. Gan:** Validation, investigation. **X. Qin:** Conceptualization, resources, data curation, supervision, funding acquisition, validation, investigation, project administration, writing–review and editing.

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Note

Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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