PITUITARY TUMOR RISK IN RELATION TO MOBILE PHONE USE:

A CASE CONTROL STUDY

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Interphone Study: Pituitary Tumor Analysis

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ABSTRACT

Background: The number of mobile phone users has grown explosively, which has generated mounting public concern regarding possible health hazards. This study aims to assess pituitary tumor risk as it has rarely been investigated.

Materials and Methods: A case-control study was conducted with eligible cases identified from all five university hospitals in Finland and frequency-matched controls from national population register. Controls were matched to cases by age, sex, region of residence and date of interview. A detailed history of mobile phone use was obtained by a structured interview. Several indicators of mobile phone use were assessed using conditional logistic regression.

Results: A reduced odd ratio was seen among regular mobile phone users (OR 0.39, 95% confidence interval, CI: 0.21, 0.72) relative to never/non-regular users, possibly reflecting methodological limitations. Pituitary tumor risk was not increased after 10 or more years since first use (OR 0.69, 95% confidence interval, CI: 0.25, 1.89).The risk was not increased in relation to duration or, cumulative hours of use or cumulative number of calls. The results were similar for analogue and digital phones.

Conclusions: No excess risk was found to be associated with self-reported short- or medium-term use of mobile phone. This is consistent with most of the published studies. However, uncertainties remained for longer duration of use, as very small proportion of study participants reported use beyond 10 years.

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RERERENCE TO THE ORIGINAL PAPER

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LIST OF COMMONLY USED ABBREVIATIONS

IARC: International Agency for Research on Cancer

RF-EMF: Radiofrequency Electromagnetic Fields

IMTS: Improved Mobile Telephone Service

ARP: Auto Radio Puhelin

NTT: Nippon Telegraph and Telephone Corporation

NMT: Nordic Mobile Telephone

GSM: Global System for Mobile Communication

ITU: International Telecommunication Union

NCRP: National Council on Radiation Protection and Measurements

UNSCEAR: United Nations Scientific Committee on Effects of Atomic Radiations

ACTH: Adrenocorticotrophic Hormone

GH: Growth hormone

TSH: Thyroid Stimulating Hormone

CT: Computerized Tomography

CBTRUS: Central Brain Tumor Registry of the United States

HRT: Hormone Replacement Therapy

ICNIRP: International Commission on Non-Ionizing Radiation Protection

SARs: Specific Absorption Rates

SEER: Surveillance, Epidemiology and End Results

1. INTRODUCTION

Over the past few decades, wireless technology including mobile phone use has rapidly increased, which has drawn attention about possible health risks-predominantly an increased risk of brain tumors because of the proximity of exposure. The International Telecommunication has estimated that the number of mobile phone subscriptions will reach 7 billion in the year 2014, which is equivalent to 95.5 percent of the world population [1]. Therefore, there is much interest in understanding the relationship between mobile phone use and brain tumors because even a small increase in risk might result large number of affected people. Mobile phone emits radiofrequency energy, a form of electromagnetic radiation which can be absorbed by the tissues closest to the phone and in May 2011, the International Agency for Research on Cancer (IARC) classified radiofrequency electromagnetic fields (RF-EMF) as 'possibly carcinogenic to humans' (Group 2B) based on limited evidence from epidemiological studies [2]. The American Cancer Society responded to IARC classification of cell phones as possible carcinogenic, stating that there could be some risk but the evidence is uncertain and needs to be investigated further and limiting cell phone use seems reasonable in the light of this uncertainty [3].

The mobile phones emit radiofrequency radiation which does not have sufficient energy to damage DNA directly [4]. It is generally agreed that radiofrequency radiation emitted by mobile phone can result in a small rise in tissue temperature of the brain and adjacent organs, but studies have shown weak evidence for related mechanisms of carcinogenesis [5]. To date, several epidemiological studies have been published reporting the effect of mobile phone use on tumor risk but most studies focused on glioma, meningioma and acoustic neuroma [6-13], with few studies focusing on salivary gland tumors, leukemia or lymphoma [14-17]. Most studies are based on case-control approach depending on participants' self-reported exposure and only few are cohort studies. Only a limited number of studies have shown some evidence of association of cell phone use and the development of brain tumors among long-term users, analogue phones and ipsilateral use [18,19], but it is uncertain whether it is a true association or due to recall bias and other methodological limitations. However, most of the studies found no evidence of

increased risk [6, 8, 9, 10]. So far, pituitary tumor risk in relation to mobile phone use has been investigated in only three studies [20, 21, 22]. A similar conclusion was drawn from the two studies that there is no association between mobile phone use and the risk of pituitary tumors [20,21], in contrast another study found a raised relative risk in short-term mobile phone users with duration less than 5 years, but no evidence of trend with increasing duration of use [22].

In the late 1990s, several expert groups recommended research on the possible health effects of mobile phone use. As a result, the International Agency for Research on Cancer (IARC) coordinated a feasibility study in 1998 and 1999 and found that an international study to investigate the effect of mobile phone use and tumor risk would be feasible. A collaborative case-control study, the INTERPHONE study on brain tumors and mobile phone use was initiated in 2000 to increase the knowledge on possible health effects of mobile phone use in 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK) around the world coordinated by the IARC [23]. Interphone study is the largest case-control study of mobile phone use and brain tumors so far and includes the largest number of users with at least 10 years of exposure.

This population based case-control study with 80 pituitary tumor cases and 240 controls was conducted as part of the Interphone study. The aim of this study was to evaluate the risk of pituitary tumor in relation to mobile phone use and specifically to assess pituitary tumor risk in relation to several indicators of mobile phone use such as years since first use, total duration of use, cumulative number of calls and cumulative hours of use. For comparison, we also evaluated the risk associated with analog and digital phone.

2. LITERATURE REVIEW

In this chapter, author has reviewed a collection of research publications that are relevant and important in this thesis. The aim of this literature was to find whether there are similar researches related to the mobile phone use and brain tumors. Also, other related concepts that could be useful in this thesis are presented.

2.1 Mobile phone

2.1.1 History of mobile phone

The development of the wireless communication system began with the use of 'Walkie-talkies' during the Second World war in the 1930s to enable contact between foot soldiers and headquarters [24]. In 1946, AT-&-T and Southwestern Bell introduced the first American commercial radiotelephone service meant to connect mobile users in cars and the public fixed network [25]. Ericsson, a Swedish multinational provider of communications technology and services, introduced the world's first fully automatic mobile telephone system in 1956 which was commercially released in Sweden, which opened the way for today's mobile broadband networks [26]. The Improved Mobile Telephone Service (IMTS) launched by the Bell System in the 1960s offered direct dial rather than connecting through an operator and the first analog cellular systems were based on IMTS [27]. These systems were not cellular and were very expensive. One of the first and successful public commercial mobile phone networks was Finland's ARP network (Auto-radio puhelin in Finnish or car radio phone in English) launched in 1971. ARP is also considered as a zero-generation cellular network being slightly above limited coverage networks [28]. The first hand-held mobile phone was introduced by John F. Mitchell [29] and Dr. Martin Cooper of Motorola in 1973 using around 2 kg handsets [30]. Prior to 1973, cellular mobile phone technology was only limited to phones installed in car and other vehicles.

Wireless communication systems have been classified into several generations: First Generation (1G), Second Generation (2G), Third Generation (3G) and Fourth Generation (4G).

First Generation (1G): First generation of wireless telephone technology is analog telecommunications. In 1979, the world's first mobile phone network was launched into commercial production in Tokyo, Japan by Nippon Telegraph and Telephone Corporation, commonly known as NTT. This was followed by Nordic Mobile Telephone (NMT) in the Nordic countries in 1981. This was the first mobile phone technology allowing international use of the mobile phone or 'roaming'. The analog first generation mobile telephone was able to carry voice only and was replaced by 2G digital telecommunications [31].

Second Generation (2G): In addition to the voice service of analog phone, the second generation introduced short message service (SMS), i.e. text messages. It also introduced features to download ringtones and games. The second generation mobile telephony were commercially projected on Global System for Mobile Communications (GSM) standards and the world's first commercial GSM network was launched in Finland in 1991 [32].

Third Generation (3G): The third generation (3G) pre-commercial Wideband Code Division Multiple Access (WCDMA) trail network was launched by NTT DoCoMo in Japan, Tokyo in 2001 and then spread to Europe and USA in 2002 [33]. The technology is founded on International Telecommunication Union (ITU) which belongs to the IMT-2000. The 3G technologies are widely used due to enhanced security and encryption features. It has improvements in screen displays and the ability to handle multimedia data, such as graphics and video streaming.

Fourth Generation (4G): After the success of ITU defined IMT 2000 (3G) systems, ITU-R launched the IMT advanced (4G) initiatives [34]. 4G is better described as MAGIC (mobile multimedia, any-time anywhere, global mobility support, integrated

wireless solution, and customized personal service). 4G is intended to deliver extremely high quality video, show live image (stream video) and allow faster data transfer [35].

2.1.2 Expansion of mobile phone use

Mobile phones have become ubiquitous in our society. The number of mobile phone users has risen sharply since the early 1990's when the first digital mobile phones were introduced [36]. According to the estimation of International Telecommunication, the global penetration of mobile phone subscriptions will reach 7 billion in the year 2014 [1].

For a long time, Finland remained as one of the most advanced markets for mobile services. The number of telecommunication subscriptions in Finland quadrupled in 20 years. In 1988, total telephone subscriptions in Finland were about 2.6 million including 140,000 mobile phone subscriptions. At the end of 2008, there were over 10 million telecommunication subscriptions, fixed telephone network subscriptions numbered approximately 1.7 million, broadband subscriptions nearly 2.1 million and mobile phone subscription taking the highest position i.e. 6.9 million which is equal to 130 subscriptions per 100 populations. [37]. By the end of 2012, the number of mobile network subscriptions was 9.3 million [38]. Apart from mobile telephones and their base stations, the demand for other wireless services (radio, microwave ovens, broadcasting radio and television signals, radar and other wireless networks) has been growing rapidly among general public. Among all, mobile phones are of greater concern in terms of their safety and potential health hazards specifically due to short-term or long-term exposure to radiofrequency (RF) radiation as mobile phones are used very close to the head and neck.

Mobile phone use has been increasing dramatically as new technologies and applications are continually evolving such as text messaging, internet access, cameras,

calendars, music, email combined with standard telephone functions. It has become a social and cultural phenomenon [39] to send or receive text messages, send or receive email, download applications, get directions or location based information, listen to music, participate in video call or video chat [40]. Moreover, mobile phones have important contributions to narrow the gap in telephone usage between highly developed and less developed countries [41]. Interestingly, several studies have indicated that text messaging can help college students to quit smoking successfully [42]. In addition, cell phone facilitates communication with health care professionals where face to face communication is impossible [43].

2.2 Brain tumors

2.2.1 Definition and histological distribution of brain tumors

Tumors are defined according to their histology and location. In this thesis, the term 'brain tumor' is used to cover tumors occurring in the central nervous system (CNS), such as gliomas, meningiomas, acoustic neuromas and pituitary tumors even though the tumors are not always histologically originated from brain cells such as meningiomas originating from the meninges.

The most common primary brain tumors are gliomas and meningiomas each accounting for one third of all primary CNS tumors. Nerve sheath tumors account for 9% of all tumors (acoustic neuromas account for 63% of all nerve sheath tumors). Other primary CNS tumors include pituitary tumors (13%), lymphomas less than 3% and craniopharyngiomas less than 1%. [44]

2.2.2 Incidence of brain tumors

The burden of cancer varies across countries according to differences in risk factors, detection practices, and availability of treatment, age structure and completeness of reporting [45]. A large number of reports have indicated an increasing incidence of brain tumor from the late 1970s to early 1990s in the elderly [46, 47, 48,49,50] and in children [51, 52,53]. The exact reason and mechanism for this increasing trend is still unclear but concurring with the introduction and widespread use of improved diagnostics. Computerized tomography (CT) scanner was used for the first time in University hospital in Tokyo in 1975 and became widely available in the following two decades [54].

A study, summarizing the results from the U.S National Council on Radiation Protection and Measurements (NCRP) and United Nations Scientific Committee on Effects of Atomic Radiations (UNSCEAR) found that in United States, the frequency of diagnostic radiological examination increased by 10 fold during 1950-2006. Worldwide, the frequency of CT scanning increased from one to three procedures per 1000 population during 1977-1980 to about 35 procedures per 1000 population during 1997-2007 [55]. Among elderly North Americans, two fold increases in brain cancer incidence was observed within 2 decades and they identified CT scan and MRI as a key factor responsible for that observed trends [56].

For recent trends, epidemiological studies have mixed findings, some studies report increasing trend [57, 58,59] where as other report decreasing [60,61].

There is geographical variation in the incidence rates of brain tumors. The incidence rate for malignant brain tumors in Japan is less than half of that in Northern Europe [62]. The worldwide incidence rate of primary malignant brain and CNS tumors in 2012 was 3.4 per 100,000. The incidence rates tend to be higher in more developed countries (5.1 per 100,000) than in less developed countries (3.0 per 100,000) [63]. This may also be caused by difference in both diagnosing and registering cases as well as in access to health care.

Malignant gliomas are 40% more common among men than among women [64]. One of the studies has reported an increasing trend of gliomas in Nordic countries, however; the increase in the incidence was less than 1% (0.6% for men and 0.9% for women) for the years 1969-1998 [65]. Another similar study from 1974-2003, found even less pronounced increase for gliomas (0.5% for men and 0.2% for women) [66].

Unlike gliomas, meningiomas are more common among women than among men [67,68]. In the analysis of 134,509 primary CNS tumors across the whole of England from 1979 through 2003, a statistically non-significant annual increase of approximately

1% was reported for young people (0-24 years) in meningioma incidence. In contrast, a significant increase of 3% was found for the elderly (over 65 years). [69]

Brain tumours were the 11th most common cancer types among males and 8th among female in Finland in 2012. According to Finnish cancer registry, age-adjusted incidence rates of cancer per 100,000 person-years in 2012 for male was 11.0 and for female 13.2 [70].

2.2.3 Classification and incidence of pituitary tumors

Pituitary tumors are classified as either micro-adenomas (less than 10mm in diameter) or macro-adenomas (equal or greater than 10mm) [71]. Furthermore, they are classified as functional (prolactin producing, Adrenocorticotrophic (ACTH) producing, Growth hormone (GH) producing, Thyroid Stimulating Hormone (TSH) producing, glycoprotein producing) or non-functional depending on their hormonal activity [72]. About 30% of pituitary adenomas are prolactinomas, 15% are GH producing, 10% are ACTH producing, 10% are glycoprotein producing, and less than 1% secrete TSH. About 25% of pituitary tumors are non-secretory adenomas [73].

Most of the epidemiological studies have focused on glioma, meningioma, acoustic neuroma through case-control studies, cross-sectional studies, cohort studies and meta-analysis but pituitary tumors have rarely been investigated [21]. Due to the benign nature of pituitary tumors, most cancer registration systems do not record it, therefore data on the incidence, prevalence and trend of pituitary tumor is very limited [72].

Although classically considered to be rare, pituitary tumors account for approximately 13% of all primary brain tumors, being the third most common primary brain tumor in adults after meningiomas and gliomas [74]. The peak incidence of pituitary tumors

occur at age 30-60 years, earlier in women (20-45 years) than in men (35-60 years), as women are more sensitive to hyper-prolactinemic effect such as amenorrhea [75,76]. Some studies have reported higher incidence of pituitary tumors among American blacks compared with whites [75,77], however some disclose no racial difference in incidence rates [78].

In a descriptive study of primary brain tumors and central nervous system tumors, Central Brain Tumor Registry of the United States (CBTRUS) with 5 years of incidence data from (1990-1994) found that pituitary tumors accounted for 9.1% of all brain and CNS tumors, occurring at an incidence rate of 8 per 100,000 person-years [78].

In a cohort of 1010 women and 1269 men with pituitary adenomas, in Swedish Cancer Registry between 1958 and 1991, observed significant increase in the age-standardized incidence of pituitary adenomas from approximately 6 cases/million inhabitants in 1958 to 11cases/million inhabitants in 1991, which suggest a doubling in the annual incidence of pituitary adenoma [79]. Existing epidemiological data suggest that the incidence of pituitary tumor is rising but no conclusion can be derived from the current literature and the true incidence of pituitary tumor is difficult to establish with certainty.

2.2.4 Etiology of brain tumors

Just as in the case of many other cancers, the etiology of all subtypes of brain tumor remains largely unknown and research into it is ongoing but studies do suggest that many different factors may be associated with them.

The well-established etiological factors for all types of brain neoplasm are high-dose ionizing radiation with most of the evidence coming from the survivors of the atomic bomb explosion in Japan [80] and a report from childhood cancer survivor study who

received cranial radiotherapy [81]. Survivors of the atomic bomb in Hiroshima and Nagasaki have been studied for different cancer types following exposure from blasts. A statistically significant dose response was observed for all nervous system tumors combined and a clear suggestion of a dose response for schwannoma was seen. About 4 of the 34 pituitary tumors were estimated to be related to radiation exposure. [80] Moreover, the association between ionizing radiation exposure and the risk was found to be stronger for meningiomas than for gliomas [62]. The largest study of CNS tumors in survivors of childhood cancer also found that the risk of meningioma was strongly and linearly related to dose of radiation [81].

A small proportion of brain tumors are also related to rare hereditary conditions such as neurofibromatosis 1 and 2 (NF1 and NF2), tuberosis sclerosis, Cowden's disease, von Hippel-Lindau disease and less frequently Li-Fraumeni syndrome, Turcot's and Gorlin's syndrome [82]. Certain inherited syndromes such as tuberous sclerosis, neurofibromatosis type 1 and 2, nevoid basal cell carcinoma syndrome, and syndromes involving adenomatous polyps, account for approximately 1–2% of all tumours [83]. However, the limited findings available so far have failed consistently to identify life time risk of brain tumors for carriers of these syndromes. A large pooled analysis found an increase in a twofold risk of glioma in first degree relatives of glioma patients [84].

No association between smoking or alcohol consumption and increased risk of intracranial tumors has been reported [83]. Maternal smoking during pregnancy does not appear to be strongly linked to brain tumours according to the meta-analysis of 6566 subjects from 12 epidemiological studies [85] However, a later prospective study supported the role of maternal smoking during pregnancy in the etiology of childhood brain tumors [86].

A meta-analysis on the association between excess body weight and the risk of meningioma has shown that meningioma risk is higher in obese (body mass index: BMI 30+) females, compared with healthy weight (BMI 18.5-25) females but due to limited number of studies, the association remains unconfirmed [87].

N-nitroso compounds formed by the reaction of amines and amides have been identified as potent nervous system carcinogens in animal models [62]. For humans, assessing N-nitroso compound exposure is difficult because they are extremely common in endogenous and exogenous sources. Studies of diet and vitamin supplementation have provided mixed support for the hypothesis that dietary N-nitroso compounds might influence the risk of either childhood or adult brain tumors [62,83,88]. In some studies, a consistent inverse association was observed for a combined intake of coffee and tea and the risk of glioma but needs to be confirmed in detail [89,90]

A large prospective study with over a million postmenopausal women to examine the relation between the use of hormone replacement therapy (HRT) and the incidence of central nervous system tumors (CNS) found that the incidence of CNS tumors was slightly (statistically significantly) increased in the current users of HRT particularly in the users of estrogen only therapy when compared to never users. In the analysis by tumor type, there was no significant difference between tumors specified as glioma, meningioma and acoustic neuroma [91].

In experimental animal models, brain tumours can be induced by a number of different viruses such as retroviruses and adenoviruses but there is little evidence for this occurring in humans. In utero infections with influenza and chicken pox have been cited as a risk factor but the association is not so strong [92].

Serious head trauma has long been suspected to be related to some type of brain tumors. Some studies have shown an apparently increased risk during the first year of serious head injury which might be due to increased early detection but does not show any association in subsequent years [93].

2.3 Electromagnetic radiation

2.3.1 Nature and sources of electromagnetic radiation

Electromagnetic radiation is ubiquitous in modern society. There are many natural and man-made sources of electromagnetic radiation. Natural sources include earth's magnetic field and man-made sources encompass radio stations, mobile phone base stations, TV antennas, microwaves, radars and other electrical appliances [94]. Radiofrequency (RF) radiation is a form of electromagnetic radiation. Within the electromagnetic spectrum, there is some variation in the classification of frequency bands but typically radiofrequency electromagnetic fields (RF-EMF) cover the frequency range from 100 KHz to 300GHz [95].

Exposure to ionizing radiation such as x-rays and gamma rays is known to cause DNA damage by breaking chemical bonds in molecules [96]. However, no consistent evidence has been demonstrated that non-ionizing radiation increases the risk for any of the brain or other head tumors [97]. The International Commission on Non-Ionizing Radiation Protection (ICNIRP) formulated guidelines in limiting exposure to protect people from the suspected harmful effects of RF radiation that covered the frequency range up to 300 GHz [98].The guidelines published in 1998 were revised and in 2010, they issued new guidelines for the frequency range 1Hz to 100 kHz which replaces the low-frequency part of the 1998 guidelines [99]. The ICNIRP guidelines are based on an analysis of all relevant scientific literature, including both thermal and non-thermal studies. The harmful effects are due to the temperature rise in tissue after the absorption of RF radiation. The guidelines include a substantial safety margin for limiting public exposure as the public exposure limit with regard to RF caused temperature rise has been set at one tenth or below of the value where harmful effects can occur. [98]

2.3.2 Mobile phone as a source of electromagnetic radiation

Currently, mobile phones are one of the most important sources of radiofrequency radiation besides broadcasting radio and television signals, microwaves and other electrical appliances. Mobile phones emit RF-EMF during transmission phase (i.e. when speaking during a phone call), which are non-ionizing and cannot cause damage to DNA (mutations). However, they have some thermal effects in contacts with the human body, raising the temperature in the tissues. This is the only established mechanism for biological effect of radiofrequency radiation. If there is an effect of mobile phone use at all, then it would be based on tumor promotion or progression rather than initiation [100].

Specific absorption rate (SAR), measures the level of exposure to mobile phone radiation and it is expressed as W/kg (power per unit mass of body tissue). The SAR distribution appears to decrease very rapidly with increasing depth, on average to a tenth with in the 5cm distance of brain tissue [101]. ICNIRP has given recommendations for SAR value limits to such a level that the excess temperature rise remains below 1degree Celsius. The SAR level has been set to 0.08 W/kg for whole body exposure for the general public, 2W/kg for local exposure to the head and torso, and 4W/kg for local exposure to the limbs. A maximum SAR of 2 W/kg has been set as the highest value for localized exposure from mobile phone [98]. However, the SAR from a mobile phone varies with a range from about 0.0001 to 2W/kg. This variation appears due to the several determinants of SAR value such as the output power of the phone, phone model, positioning of the phone, distance between the phone and the exposed tissues and network characteristics [102].

In Europe, two principal mobile phone network types have been used: analogue (Nordic Mobile Telephone, NMT) which operates on 450/900 MHz frequencies and digital (Global System for Mobile Communications, GSM) operating at 900/1800 MHz. In addition to NMT and GSM telephones, third and fourth generation mobile phones have

been introduced; however, only exposure to NMT or GSM mobile phones are addressed in this thesis.

The NMT and GSM systems operate in different power level as NMT phones emit radiation at a constant level (1W), whereas GSM use pulsed signals. The maximum transmission power of GSM phones is 0.25 W at 900 MHz frequency and 0.125W at 1800 MHz frequency. The GSM system uses adaptive power control (APC) to reduce output power. A recent study has shown power reduction to around 50% (ranging from 35 to 70%, depending on the country) of the maximum power levels in both 900 and 1800MHz frequency bands. [103]

Some expert groups have mentioned that the use of hands-free devices minimizes exposure by limiting the number and duration of phone calls [87]. In addition, there will be lower exposure to radiofrequency fields than someone holding the handsets against their head. The use of hands-free device considerably reduces the SAR in the head by a factor of 20–100 [102].

2.4 Mobile phones and brain tumors

There have been numerous studies to examine the association between mobile phone use and the risk of brain tumours [3-14, 18-22,35,46-50,54-62,64-67,69,95,97,100-103]. Most studies are based on case-control design [6-13, 18-22, 35] and only few are cohort studies [105, 106]. Most of the studies rely on participants' self-report for exposure assessment, with few exceptions using telephone company records [7,105,107].

The largest case-control study of mobile phone use and brain tumor, the INTERPHONE study, reported a reduced odds ratio for glioma [OR 0.81; 95% CI: 0.70–0.94], meningioma (OR 0.79; 95% CI: 0.68–0.91) and acoustic neuroma 0.85 (95% CI: 0.69-1.04) between ever having been a regular mobile phone user and a never regular user. Although, the risk was not elevated for longer duration of use (>10 years), there were some indications of an increased risk of glioma in the temporal lobe than any other lobes of the brain at the highest exposure levels but biases such as recall bias and error prevented causal interpretation [108].

A large nationwide cohort study to investigate cancer risk among Danish mobile phone users linked billing information for more than 358,000 cell phone subscribers between 1982-1995. After following for up to 21 years, no association was found between mobile phone use and the incidence of glioma, meningioma or acoustic neuroma among either short-term or long-term users. [105,106]

A large prospective study of middle-aged UK women, the Million Women Study, found that mobile phone use was not associated with an increased risk of glioma and meningioma. However, an increased risk (RR 1.88, 95% CI: 1.14–3.11) was found for acoustic neuroma in those who had used a mobile phone for more than 5 years. This significantly increased risk among long-term users remained unconfirmed, as the risk for acoustic neuroma was not significantly increased when the results were combined with previous Danish prospective study. [22]

Gliomas, meningiomas and acoustic neuromas are among the most commonly investigated brain tumors in relation to mobile phone use. Pituitary tumours have not been paid as much attention as gliomas and meningiomas. A previous analysis of Japanese Interphone study reported no association between mobile phone and pituitary tumors [20]. Another study, based on 291 pituitary tumor cases and 630 controls from Southeast England also found no association with any aspect of mobile phone use [21]. A recent study, with a large UK cohort of middle aged women found increased relative risk for pituitary tumors among short-term users (duration less than 5 years) (RR

2.31,95% CI:1.31-4.06), but there was no evidence of increasing trend in risk with increasing duration of use [22].

The Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute, which tracks cancer incidence in the United States, shows that despite the sharp increase in mobile phone use in the U.S between 1987 and 2008, the overall age-adjusted incidence of brain cancer did not increase [109]. Similar results have been reported from the Nordic countries [12, 66] and the UK [35].

It can be concluded from all the literature that there is a lack of evidence of an increased risk of any types of brain tumor associated with mobile phone use. However, for slow-growing tumors, the latency period is still too short to draw valid conclusions. A large prospective cohort study of mobile telephone users (COSMOS) was launched in 2010 in five European countries to monitor possible health risks related to long-term mobile phone use among a large group of mobile phone users. It will take some time to obtain results from this study as the mobile phone users will be followed for 20^{+} years [110].

2.5 Mobile phone use and other cancers

Apart from glioma, meningioma, acoustic neuroma and pituitary adenoma, some epidemiological studies have also focused on salivary gland tumors, leukemia or lymphoma, testicular cancer and intra-temporal facial nerve tumors.

Two population-based case control studies in Denmark and Sweden concluded that mobile phone use is not related to an increased risk of parotid gland tumors [111]. Similarly, one study with 69 cases and 262 randomly recruited controls found no association (OR 0.8, 95% CI, 0.4-1.5) between mobile phone use and parotid gland

tumor for light to moderate users, but provided little information on long-term users [112].However in contrast, Israeli INTERPHONE study with 402 benign and 58 malignant incident cases and 1,266 controls in 2001-2003 suggested a positive association between cellular phone use and parotid gland tumors [16].

Regarding lymphoma, no consistent pattern of an increased risk was found [15,113]. There have been only a few studies for leukemia. A case-control study in South East England found no association between mobile phone use and leukemia. A non-significantly raised risk (OR 1.87, 95% CI, 0.96-3.63) was found in heavy users [17]. Regular cellular phone use does not appear to be associated with intra-temporal facial nerve tumor [114] or testicular cancer [115].

2.6 Results of the meta-analysis from previous studies

Author has noted some reports of the published meta-analysis regarding the effect of the mobile phone use on brain tumor risk and is presented below:

First Author (last name, year)	No of studies	OR, glioma (95 % CI)	OR, meningioma (95% CI)	OR, acoustic neuroma (95% CI)	OR >10 yrs of use (95% CI)	Comments
Lahkola 2006 [116]	12	0.96 (0.78-1.18)	0.87(0.72-1.05)	1.07(0.89-1.30)	-	No indication of substantially increased risk of intracranial tumors from mobile phone use for a period of at least 5 years.
Hardell, 2008 [117]	10-glioma 7-meningioma	0.9(0.8-1.1)	0.8 (0.7-0.99)	0.9(0.7-1.1)	1.2(0.8-1.9) for glioma 1.3(0.9-1.8) for meningioma and	Provided a consistent pattern of association between

	9-acoustic neuroma				1.3(0.6-2.8) for acoustic neuroma	mobile phone use and ipsilateral glioma and acoustic neuroma using ≥10 years latency period
Kan, 2008 [118]	9	low grade glioma 1.14 (0.91-1.43) high grade glioma 0.86 (0.70-1.05)	0.64 (0.56-0.74)	0.96(0.83-1.10)	From 5 studies-1.25(1.01-1.54)	No overall increased risk of brain tumors among mobile phone users. Elevated risk after long term exposure awaits confirmation by future studies
Ahlbom, 2009 [97]	14-Glioma 14-meningioma 13-Acoustic neuroma	Short term use: 1.0 (0.9–1.1	Short term use: 0.8(0.7–0.9)	Short term use 1.0 (0.7-1.4)	For glioma: 1.1 (0.8–1.4) For meningioma: 1.2 (0.7–2.2). For Acoustic neuroma: 1.4(0.7-2.5)	laterality analyses were also covered but these were difficult to interpret due to methodological problems such as recall bias
Repacholi 2012 [119]	8 studies for glioma 4-meningioma 8 for acoustic	Short term use (1–6 years) 1.03 (0.86–1.24)	0.82 (0.72–0.94)	0.99 (0.70-1.41)	For glioma 1.40(0.84-2.31) For meningioma 1.25, (0.51–3.10) For acoustic	There is very limited data available for long-term use of mobile phone. All results are

	neuroma				neuroma 1.37(0.74–2.52)	obtained after combining Hardell et al. studies and Interphone studies
Lagorio, 2014 [120]	47 studies (17 on glioma, 15 on meningioma, 15 on acoustic neuroma	No increased risk was observed among short term and medium term users in any meta-analysis	Decreased risk was observed in almost all meta-analysis	Moderate to high degree of heterogeneity across studies detected. The combined relative risks tend to increase with increasing time since start of use	The combined relative risks ranged between 0.98 (0.75–1.28) and 1.11 (0.86–1.44) for meningioma For glioma: 1.19 (95% CI 0.86–1.64) and 1.40 (0.96–2.04) For Acoustic Neuroma: 1.14 (0.65–1.99) to 1.33 (0.65–2.73)	47 studies were classified in to 5 groups (i.e US studies, Finnish studies, Örebro series,Interphone study and Danish cohort study) Detected a moderate to high degree of heterogeneity across studies of glioma and acoustic neuroma and no or low heterogeneity across studies of meningioma

A meta-analysis of 11 long-term epidemiological studies examining long-term cell phone use (≥10 years) and the risk of developing brain tumor including 'Hardell group studies' and 'Interphone group studies' gave an overall ORs (95% CI) for glioma (OR, 1.3; CI, 1.1-1.6), meningioma(OR, 1.1; CI, 0.8-1.4), acoustic neuroma (OR, 1.3; CI, 0.97-1.9) [121].

Another meta-analysis to evaluate the brain tumor risk among long-term users of cellular telephones with 2 cohort studies and 16 case control studies found increased

odd ratio especially for ipsilateral exposure, acoustic neuroma (ORs 2.4;95% CI 1.1-5.3) and for glioma(ORs 2;95% CI 1.2-3.4) [122].

3. WORK DESCRIPTION

My interest in cancer research began when I was doing my undergraduate degree. Several years later, I got chance to fulfill this desire, and currently I am pursuing this interest as a degree student under the supervision of Prof. Anssi Auvinen. My first true research experience began as a summer apprentice during June, July and August 2014. I feel really lucky, proud, privileged and honored to be offered work placement for three months on University premises and stretch myself personally and professionally. Basically, I was working in Interphone project which is the largest case-control study on the topic, aiming to investigate whether the mobile phone use increases the risk of intracranial tumors. It has cemented my interest and I chose to write my thesis on the same project focusing on pituitary tumor risk.

I was provided with pituitary tumor case list and the list of controls. At first my task was to select suitable cases that meet our study pre-requisites. Out of the 85 interviewed cases, I excluded 5 cases because they did not meet the inclusion criteria. We had 1232 controls, out of which we selected 240 controls matched to cases by age, sex, region of residence and date of interview. The total number of study subjects included in the analysis was 320. Our biostatistician Jani Raitanen helped me throughout the process, then data sets were ready for analysis. Analyses were almost completed within 2 months, however a few were added later on as per suggestions from co-authors. The software, Stata that I used was totally new for me; I was familiar with SPSS only. At the beginning I was afraid of using new software but Jani kept it as simple as possible. It was such a great opportunity to learn basic analysis in Stata. Now, I have developed confidence to work on this software.

Then I started writing report and preparing manuscript for journal article. I went through lots of previous related articles and gain some ideas about those studies and my supervisor was available all the time to guide, encourage and motivate me during data analysis, interpretation and writing paper. He arranged all the specific tools for me and kept me in track for the whole period.

Being a presenting author, I had huge responsibilities to come up with the well-polished manuscript. Never having been exposed with such domain, I was challenged but equally excited to work with expert co-authors. Tiina Salminen and Anna Lahkola have provided intellectual input for manuscript correction. The comments and feedbacks were really very important and useful for me. It was the collective continuous effort of the author and co-authors to complete this manuscript successfully. Now, we have submitted manuscript for Acta Oncologica, and we are looking forward for receiving reviewer comments and eventually its publication.

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