EXPOSURE TO LOUD NOISE AND RISK OF ACOUSTIC NEUROMA

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Colin G. Edwards, M.S.

* * * * *

The Ohio State University

2007

Dissertation Committee:

Professor Randall A. Harris, Co-Adviser
Professor Judith A. Schwartzbaum, Co-Adviser
Professor John M. Crawford

Approved by

Co-Advisers
Graduate Program in Public Health
This dissertation presents three related investigations that evaluate the previously reported association between loud noise exposure and the risk of acoustic neuromas, as well as the proposed biological basis for the association. The goal of the first investigation was to examine further the role of loud noise in acoustic neuroma etiology. In a population-based case-control study conducted from 1999-2002 in Sweden, reports of occupational and nonoccupational loud noise exposure of 146 acoustic neuroma cases and 564 controls were compared. Individuals reporting loud noise exposure from any source were found to be at increased risk for acoustic neuromas. The findings of an increased risk of acoustic neuromas with loud noise exposure support previous research.

The goal of the second investigation was to further examine the association between noise exposure and acoustic neuroma using an objective measure of exposure. A total of 793 acoustic neuroma cases were identified between 1987 and 1999 from the Swedish Cancer Registry, to which 101,756 controls were frequency matched. Occupational information, available for 599 of the cases and 73,432 of the controls, was obtained from censuses and linked to a job exposure matrix. Of three studies of noise exposure and acoustic neuroma risk to date, this is the first to use a job exposure matrix.
to assess exposure. Contrary to previous study results the findings do not demonstrate an increased acoustic neuroma risk related to occupational noise exposure.

A mechanism of acoustic neuroma tumorigenesis during the cellular repair process following acoustic trauma has been proposed, whereby cellular division results in DNA replication errors which may in turn lead to chromosomal changes essential for neoplastic transformation. In the third investigation, an extensive literature search was conducted to evaluate the biological plausibility of this hypothesis. The tumor typically involves the vestibular rather than the acoustic division of the eighth nerve, however intralabyrinthine and cochlear nerve schwannomas have been reported. Additionally, evidence of vestibular damage in rodents has been demonstrated following acoustic trauma. The proposed hypothesis is therefore plausible, however further research is needed to elucidate the precise biological basis for the association between loud noise and acoustic neuromas.
Dedicated to my wife and children
ACKNOWLEDGMENTS

I wish to thank Professor Judith Schwartzbaum for her support, enthusiasm, and knowledge of epidemiologic methods, all of which were invaluable during my entire doctoral training. I also thank her for providing me with the opportunity to collaborate with researchers at the Karolinska Institute during my doctoral dissertation research. Additional thanks go to Professor Randall Harris for his advice in the field of cancer epidemiology and for his encouragement at the time of my doctoral candidacy exam and during the completion of my dissertation. Many thanks are also due to Professor John Crawford for his guidance, encouragement, and friendship.

In addition, I extend gratitude to Professors Maria Feychting and Anders Ahlbom at the Institute of Environmental Medicine at the Karolinska Institute in Stockholm, for twice inviting me to the Karolinska Institute to obtain and begin the analysis of my two dissertation research data sets. I also thank Drs. Stefan Lönn and Ulla Forssén, former doctoral students at the Karolinska Institute, for their guidance and advice. The advice and support of Professor Thomas Prior is also appreciated. Thanks also go to Professor Clive Edwards for his insightful comments on the final draft of my dissertation and to Ms. Lynn Higginbotham for her administrative support.

Lastly, but by no means least, my immeasurable thanks to my wife Anne for her unwavering support, understanding, and patience during the almost eight years of my
part-time doctoral studies. Without her support for my trips to Sweden and my late nights at the library, my doctoral studies and this dissertation research would not have been possible.
VITA

1987 – 1992 .................................................. B.S. Microbiology,
The Ohio State University

1993 – 1995 .................................................. M.S. Preventive Medicine,
The Ohio State University

1995 – 2005 .................................................. Research Associate, Comprehensive Cancer Center, The Ohio State University

2005 – present .............................................. Senior Research Specialist, Comprehensive Cancer Center, The Ohio State University

PUBLICATIONS


FIELDS OF STUDY

Major field of study: Public health

Area of specialization: Cancer epidemiology

Minor field of study: Molecular pathology
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>ii</td>
</tr>
<tr>
<td>Dedication</td>
<td>iv</td>
</tr>
<tr>
<td>Acknowledgments</td>
<td>v</td>
</tr>
<tr>
<td>Vita</td>
<td>vi</td>
</tr>
<tr>
<td>List of Tables</td>
<td>xiii</td>
</tr>
<tr>
<td>Chapters:</td>
<td></td>
</tr>
<tr>
<td>1. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Need for the Present Studies and Overview of Acoustic Neuromas</td>
<td>1</td>
</tr>
<tr>
<td>1.2 Sporadic Acoustic Neuromas and Bilateral Neurofibromatosis</td>
<td>4</td>
</tr>
<tr>
<td>1.3 Histopathology</td>
<td>7</td>
</tr>
<tr>
<td>1.4 Natural History</td>
<td>9</td>
</tr>
<tr>
<td>1.5 Clinical Presentation</td>
<td>13</td>
</tr>
<tr>
<td>1.6 Diagnostic Modalities</td>
<td>16</td>
</tr>
<tr>
<td>1.7 Management</td>
<td>19</td>
</tr>
<tr>
<td>1.8 Incidence, Age and Sex Distribution</td>
<td>22</td>
</tr>
<tr>
<td>1.9 Risk Factors</td>
<td>24</td>
</tr>
<tr>
<td>1.10 References</td>
<td>31</td>
</tr>
<tr>
<td>2. Exposure to Loud Noise and Risk of Acoustic Neuroma</td>
<td>37</td>
</tr>
<tr>
<td>2.1 Abstract</td>
<td>32</td>
</tr>
<tr>
<td>2.2 Introduction</td>
<td>33</td>
</tr>
<tr>
<td>2.3 Materials and Methods</td>
<td>34</td>
</tr>
<tr>
<td>2.3.1 Study Design and Population</td>
<td>34</td>
</tr>
<tr>
<td>2.3.2 Acoustic Neuroma Case Ascertainment</td>
<td>34</td>
</tr>
</tbody>
</table>
2.3.3 Controls ................................................................. 35  
2.3.4 Data Collection and Loud Noise Exposure Assessment ..... 36  
2.3.5 Statistical Analysis .................................................. 37  
2.4 Results ............................................................................. 38  
2.5 Discussion .......................................................................... 47  
2.5.1 Loud Noise Exposure and Risk of Acoustic Neuroma ..... 47  
2.5.2 Other Risk Factors ..................................................... 48  
2.5.3 Diagnostic Delay ......................................................... 49  
2.5.4 Acoustic Trauma and Tumorigenesis .......................... 50  
2.5.5 Recall and Selection Bias ............................................ 51  
2.5.6 Conclusion .................................................................... 52  
2.6 Acknowledgments ............................................................ 52  
2.7 References ........................................................................... 53  

3. Exposure to Occupational Noise and Risk of Acoustic Neuroma ........ 56  
3.1 Abstract ............................................................................ 56  
3.2 Introduction ......................................................................... 57  
3.3 Materials and Methods ..................................................... 58  
3.3.1 Study Design and Population ....................................... 58  
3.3.2 Acoustic Neuroma Case Ascertainment .................... 58  
3.3.3 Controls ........................................................................ 59  
3.3.4 Census Data ................................................................. 59  
3.3.5 Job Exposure Matrix ..................................................... 59  
3.3.6 Individual Noise Exposure Assessment ...................... 60  
3.3.7 Statistical Analysis ......................................................... 62  
3.4 Results .............................................................................. 62  
3.5 Discussion .......................................................................... 69  
3.5.1 Occupational Noise Exposure and Risk of Acoustic Neuroma ......................................................... 69  
3.5.2 Comparison of Results to Prior Study of Self-Reported Noise Exposure and Potential for Recall Bias ........................................................................ 71  
3.5.3 Diagnostic Delay and the Healthy Worker Survivor Effect ................................................................. 71  
3.5.4 Misclassification of Exposure and Confounding .......... 72  
3.5.5 Conclusion ..................................................................... 74  
3.6 Acknowledgments ............................................................. 74  
3.7 References ......................................................................... 75  

4. Acoustic Neuroma: Histopathology, Natural History, and the Role of Acoustic Trauma in Tumorigenesis .................................................. 78  
4.1 Abstract ............................................................................ 78  
4.2 Epidemiology ....................................................................... 79
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3 Genetics</td>
<td>81</td>
</tr>
<tr>
<td>4.4 Histopathology</td>
<td>83</td>
</tr>
<tr>
<td>4.5 Pathology of the Vestibulocochlear Nerve</td>
<td>85</td>
</tr>
<tr>
<td>4.6 Nerve Origin of Acoustic Neuromas</td>
<td>86</td>
</tr>
<tr>
<td>4.7 Natural History</td>
<td>87</td>
</tr>
<tr>
<td>4.8 Growth Rate</td>
<td>89</td>
</tr>
<tr>
<td>4.9 Noise-Induced Mechanical Damage of the Cochlea</td>
<td>94</td>
</tr>
<tr>
<td>4.10 Acoustic Trauma in the Pathogenesis of Acoustic Neuroma</td>
<td>95</td>
</tr>
<tr>
<td>4.11 Conclusion</td>
<td>97</td>
</tr>
<tr>
<td>4.12 References</td>
<td>99</td>
</tr>
<tr>
<td>5. Summary and Conclusions</td>
<td>106</td>
</tr>
<tr>
<td>5.1 Summary of Key Study Findings</td>
<td>106</td>
</tr>
<tr>
<td>5.2 Summary of the Role of Acoustic Trauma in Acoustic Neuroma Tumorigenesis</td>
<td>107</td>
</tr>
<tr>
<td>5.3 Study Limitations and Recommendations for Future Research</td>
<td>108</td>
</tr>
<tr>
<td>5.4 References</td>
<td>110</td>
</tr>
<tr>
<td>List of References</td>
<td>111</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Selected characteristics of the 710 study participants, Sweden, 1999-2002</td>
<td>42</td>
</tr>
<tr>
<td>2.2</td>
<td>Odds ratios for acoustic neuroma according to loud noise exposure, Sweden, 1999-2002</td>
<td>43</td>
</tr>
<tr>
<td>2.3</td>
<td>Odds ratios for acoustic neuroma according to duration of loud noise exposure, Sweden, 1999-2002</td>
<td>44</td>
</tr>
<tr>
<td>2.4</td>
<td>Odds ratios for acoustic neuroma according to loud noise exposure type, Sweden, 1999-2002</td>
<td>45</td>
</tr>
<tr>
<td>2.5</td>
<td>Odds ratios for acoustic neuroma according to loud noise exposure and latency period, Sweden, 1999-2002</td>
<td>46</td>
</tr>
<tr>
<td>3.1</td>
<td>Selected characteristics of all study participants and of the study participants with information on exposure, Sweden, 1987-1999</td>
<td>65</td>
</tr>
<tr>
<td>3.2</td>
<td>Most frequent occupations with high ($\geq 85$ dB) loud noise exposure among cases and controls for men and women, Sweden, 1987-1999</td>
<td>66</td>
</tr>
<tr>
<td>3.3</td>
<td>Odds ratios and 95% confidence intervals for acoustic neuroma in relation to loud noise exposure level according to latency period duration, Sweden, 1987-1999</td>
<td>67</td>
</tr>
<tr>
<td>3.4</td>
<td>Odds ratios and 95% confidence intervals for exposure to loud noise at any time (ever) for one, two, three, or four consecutive censuses closest in time prior to reference year, Sweden, 1987-1999</td>
<td>68</td>
</tr>
</tbody>
</table>
CHAPTER 1

INTRODUCTION

1.1 Need for the Present Studies and Overview of Acoustic Neuromas

The incidence of acoustic neuromas has been increasing and this observation provided motivation for these studies of loud noise exposure as a potential risk factor for this tumor (3, 54, 57). In addition, previous studies of risk factors for acoustic neuromas have generally grouped the tumor under the broad heading of “brain tumors” and few studies have examined acoustic neuromas alone. A study of loud noise exposure as a potential risk factor for acoustic neuromas was therefore warranted. An association between occupational loud noise exposure and acoustic neuromas has been demonstrated in a study of men performed in 1989, however no subsequent studies have attempted to confirm the association (71). The previous study proposed a hypothesis that mechanical trauma may contribute to acoustic neuroma tumorigenesis (71). Further examination of the plausibility of this hypothesis was also of interest as part of this dissertation research. Additionally, loud noise exposure remains a significant public health problem, especially with the increase in the use of in-the-ear technology listening devices such as MP3 players, further supporting the need for studies of loud noise exposure and risk of acoustic neuroma.
Brain tumor registry data were not readily available in the United States and collaboration with researchers at the Institute of Environmental Medicine at the Karolinska Institute in Stockholm, Sweden provided the opportunity to analyze Swedish brain tumor data. Swedish Cancer Registry data have high coverage and accuracy, and in addition data were readily available from the continuously updated Swedish Population Registry. A large number of cases of acoustic neuroma were identified for the studies reported in Chapters 2 and 3, and controls were readily available for matching to the cases. Finally, the previous study of loud noise exposure and risk of acoustic neuroma did not report findings for nonoccupational exposure and included only men (71). The Swedish acoustic neuroma data provided both occupational and nonoccupational loud noise exposure information for both males and females, providing additional motivation for further study of this potential risk factor.

Acoustic neuroma, also known as vestibular schwannoma, acoustic schwannoma, or benign neurilemoma, is a benign tumor originating in the region of Scarpa’s ganglion at the junction of peripheral and central myelin of the of the vestibular division of the eighth cranial nerve (1-4). The seventh and eighth cranial nerves are housed in the confined bony structure of the internal auditory canal (2). The slow-growing acoustic neuroma tumor usually results from the abnormal proliferation of Schwann cells covering the superior vestibular division or the inferior vestibular or cochlear division of the nerve as it passes through the internal auditory canal (1, 5). The tumors can also originate outside the canal (6). Historically, the tumor has been termed “acoustic neuroma” although the name “vestibular schwannoma” in fact describes the tumor more accurately. In order to maintain consistency with the majority of the published literature the term
“acoustic neuroma” is used throughout this dissertation document. Schwann cells are named after the German physiologist and histologist Theodor Schwann, 1810-1882, who was the first to describe the nerve sheath cells (7). These cells are the glial or “supporting” cells of the peripheral nervous system (8). Acoustic neuromas comprise approximately 5-10% of all intracranial tumors and account for 71-90% of all tumors involving the cerebellopontine angle (1, 9). The remainder of cerebellopontine angle tumors are meningiomas and cholesteatomas (1).

1.2 Sporadic Acoustic Neuromas and Bilateral Neurofibromatosis

Acoustic neuromas present clinically as two distinct types, the bilateral hereditary type and the unilateral sporadic type (2, 10). The majority of acoustic neuromas are unilateral, however in approximately 4-5% of cases the tumors are bilateral (9, 11). In the bilateral expression of the disease, the germ cell experiences a genetic defect, whereas in the unilateral expression the defect occurs in the somatic cell (10). The hallmark of the genetic syndrome neurofibromatosis type 2 (NF2) or “central neurofibromatosis” is the development of bilateral acoustic neuromas (5, 10). In contrast, individuals with neurofibromatosis type 1 (NF1), also known as “von Recklinghausen’s neurofibromatosis” or “peripheral neurofibromatosis” rarely develop acoustic neuromas (4, 10).

Neurofibromatosis types 1 and 2 are characterized by the presence of neurofibromas and peripheral and central nervous system tumors (4). The incidence of NF1 is approximately 40 per 100,000 and that for NF2 is 1 per 33,000-40,000 (2, 4). A deletion of a tumor suppressor gene on the long arm of chromosome 22 has been
established as the cause of NF2 and the majority of these patients develop bilateral acoustic neuromas about 20 years earlier in life than those with unilateral acoustic neuromas (2, 3, 12). The disorder is inherited in an autosomal dominant manner with 95% penetrance (5, 10). However, in approximately 50% of patients with NF2 no family history is obtained and these cases are likely the result of new germline mutations (13). NF2 is also associated with an increased incidence of other intracranial tumors, such as gliomas and meningiomas, neurofibromas, and facial nerve neuromas (2, 5, 10). The gene for NF1 has been found on chromosome 17 and these patients rarely develop acoustic neuromas (4, 10). NF1 is characterized by multiple cutaneous neurofibromas and café-au-lait spots (13).

Both the sporadic acoustic neuromas and the bilateral hereditary acoustic neuromas exhibit remarkable genomic stability and are thought to be a result of the functional loss of the tumor suppressor gene on chromosome 22 (14, 15). The \( NF2 \) gene was mapped to 22q12.2 in 1986 and identical candidate \( NF2 \) genes were isolated in 1993 (13, 14). The gene encodes a protein of 595 amino acids named merlin (for moesin-ezrin-radixin-like protein), also known as schwannomin, and mutation in the \( NF2 \) gene causes loss of expression of this functional tumor suppressor protein (13, 16). It is thought that inactivating mutations of the \( NF2 \) gene may result in a truncated protein product (17). Classical merlin knockout mice have been shown to develop a variety of tumors, including highly malignant tumors, but they do not develop schwannomas (18).

The primary \( NF2 \) constitutional mutations in NF2 patients are point mutations, whereas the main causal event in sporadic acoustic neuromas are small deletions (19). It is likely that the \( NF2 \) protein is involved in intracellular signaling, modulation of cell
motility, and suppression of mitogenesis in schwannoma cells (13, 20). The mechanism of tumorigenesis acts in accordance with Knudson’s “two hit” mutation model, identical to the retinoblastoma model of carcinogenesis involving the 13q chromosomal region (15, 21). A more complete understanding of other genes whose expression are deregulated during acoustic neuroma tumorigenesis will provide better understanding of why \( NF2 \) mutation leads to tumor formation (16). The present research on loud noise exposure as a risk factor for acoustic neuromas includes only patients with unilateral, sporadic acoustic neuromas.

1.3 Histopathology

The appearance of many pathologic markers in acoustic neuromas has been described in the literature. These include Luse bodies, fibrous collagen bundles, myelin sheath irregularities, and subepithelial nerve fiber losses, all observed in the vestibule (22). The tumors have a remarkably diffuse yellow appearance, a firm consistency, and when compared to other benign intracranial tumors acoustic neuromas have the least proliferative status (7, 9, 23). It is the distal part of the eighth nerve, with Schwann cells enclosing the axons, where an overproliferation of Schwann cells leads to the formation of an acoustic neuroma (7). Acoustic neuromas can reach sizes of up to several centimeters in diameter and thus most of the cells comprising a tumor are not adjacent to the axon (24). As a result, acoustic neuroma cells can survive and proliferate in the absence of axon-derived growth factors, in a similar manner to mature, denervated Schwann cells (24). Acoustic neuromas derive their arterial blood supply primarily from the branches of the basilar arteries, as well as from branches of the vertebral arteries (9).
As the tumor grows it follows the direction of least resistance, often medially into the cerebellopontine angle, at which stage it may be of considerable size (10). As a result, an acoustic neuroma is often comprised of two parts, the stalk within the internal auditory canal and the main portion occupying the cerebellopontine angle (10).

Schwann cells are multivalent neuro-ectodermal cells which are considered homologous to oligodendroglia of the central nervous system, both of which form and maintain the myelin sheath (25, 26). The cell has a large round or elongated nucleus with a prominent nucleolus and finely distributed chromatin (25). Surrounded by basement membrane, the Schwann cell has a histological appearance marked by two prominent tissue types (25). Type A Antoni cells which are composed of a closely packed, cellular, fibrillary structure, with small spindle-shaped densely staining nuclei, and type B Antoni cells which are comprised of a less cellular, loosely arranged, reticular structure (7, 9, 23). The type B Antoni cells may contain mucinous and microcystic changes (27).

Approximately 15 percent of tumors will contain cysts, characteristic of cystic acoustic neuromas (27). The type A Antoni cells are intermingled with the type B cells, however the two cells types are generally rather well demarcated (9). The transition from type A tissue to type B tissue, or vice versa, can be abrupt or continuous (9).

The vestibular and cochlear nerves transmit sensory input regarding balance and hearing, respectively (27). The vestibulocochlear nerve measures approximately 20 mm in length from the nerve root entry zone of the brain stem to the labyrinth end organ (10). The vestibular nerve has an embryologically disordered arrangement of sheath cells that predisposes it to develop schwannomas (28). The cochlear fibers are smaller, greater in number, and darker staining than the vestibular fibers (29). However, the plane between
the cochlear and vestibular fibers is often not clear (29, 30). The fibers of both nerves originate in separate end organs and have separate central connections, however they do travel as one nerve through the posterior cranial fossa and internal auditory canal (31). The capsule typically divides the tumor from the nerves (29).

Finally, inflammation is a recurrent hallmark of acoustic neuromas on histological sections, especially in Antoni type B areas, and inflammatory components have been shown to influence benign tumor size and growth (32). In one study the degree of inflammation increased with time, which is consistent with the concept that inflammation is a degenerative change (32).

1.4 Natural History

The natural history of untreated acoustic neuromas is unpredictable (2, 78). In a study of in vivo and in vitro growth models, Charabi states that any attempt to elucidate the natural history of acoustic neuromas must have as its basis a clear understanding of the environment in which the disease develops (7). This includes an understanding of the normal anatomy and histology of the vestibulocochlear nerve, growth factors, histological changes, and factors that determine rates and patterns of tumor growth (7). It has been well documented in the literature that some tumors grow, some regress, some do not grow at all, and some display a variable pattern of growth (33, 34).

Serial radiographic studies on patients who are not surgical candidates or who refuse surgery have provided some insight into the natural history of tumor expansion (10, 35). However, factors such as loss of inhibitor regulation, local growth factors, and other cell cycle regulators that may help predict tumor growth have not yet been
identified (2, 10). Several growth factors, including nerve growth factor, glial growth
er factor, platelet-derived growth factor, basic fibroblast growth factor, transforming growth
factor-β, epidermal growth factor, and vascular endothelial growth factor have been
proposed as potentially playing a role in the pathogenesis of acoustic neuromas, but all
require further evaluation (7, 8, 16, 21, 24, 36). In addition, no consistent correlation has
been found between growth rate of acoustic neuromas and patient age or tumor size (10,
37). Studies using monoclonal antibody assays have, however, shown that clinical growth
rates will correlate with the fraction of cells found in the proliferative phase of the cell
cycle (10). Studies using the monoclonal antibody Ki-67, proliferating cell nuclear
antigen (PCNA), and DNA flow cytometric analysis have been used to examine the
growth rate and proliferative potential of acoustic neuromas (7, 38).

Some studies have shown that tumor growth rate at the start of follow-up is a
good predictor of future tumor growth rate (2, 35). Many studies have shown that the rate
of tumor growth in a given patient is consistent over the course of the disease and is
established during the first one to three years of observation (1, 2, 35). However, serial
imaging follow-up should not be terminated based solely on tumor quiescence, as some
acoustic neuroma patients do experience a delayed onset of tumor growth (39).

It has been shown that tumors larger than 20 mm are statistically more likely to
grow (2). Another study found a statistically significant inverse relationship between
tumor size and patient age (40). Other studies have reported a tendency for higher growth
rate in larger tumors and in younger patients (41, 42). Nevertheless, it is not possible to
demonstrate any pathoanatomic feature of acoustic neuroma that correlates with the
clinical course of the tumor (43, 44).
Studies have examined the proportion of acoustic neuroma patients who experienced tumor growth. Growth varied widely from 15-90% of the cases followed (34, 41, 45). In studies examining the growth rate of acoustic neuromas, the mean annual tumor growth rates ranged between 0.7 and 4.8 mm per year (33, 35, 46). Recent studies have shown that slow to medium growth of acoustic neuromas is in the range of 0.2 to 2.3 mm/year (1, 2, 10). A growth rate of >2 mm per year is seen in only 22-29% of untreated acoustic neuromas (2, 35). In comparison, a fast tumor growth rate pattern is considered to be approximately 10 mm per year (10). Methods of calculating tumor growth include tumor diameter measurement and tumor volume calculation (33). The results of two studies of tumor growth based on tumor diameter did not differ from the results based on tumor volume (47, 48). However, some studies have demonstrated more accurate tumor growth measurements using tumor volume calculations (42, 44).

It is important to note that potentially less than 1 percent of acoustic neuromas demonstrate enough growth to become clinically active, which is indicative of a very slow or arrested growth (33, 34). The emergence of gadolinium-enhanced magnetic resonance imaging (MRI) has allowed the detection of smaller and often asymptomatic tumors as small as 2 mm in diameter (35). As a result, the likelihood of finding an acoustic neuroma that would have never become clinically significant has increased enormously (33).

Tumors that exhibit enough growth to become clinically active encroach on the vestibulocochlear nerve and are likely to cause unilateral high-frequency sensorineural hearing loss, tinnitus, disequilibrium, or vertigo and as a result are at increased risk of being diagnosed. Features that can potentially distinguish tumors with fast tumor growth
from those with slow or arrested growth include the influence of growth factors such as the neuregulin-1 (NRG-1) and/or neuregulin-2 (NRG-2) proteins, as well as angiogenic factors (7, 8, 16, 20, 21, 24, 36). Also, tumor vascularity, the presence of inflammation in the Antoni type B cellular areas, a variation in basal apoptosis rates of acoustic neuroma schwannoma cells, and a possible hormonal influence may also be factors influencing tumor growth rate (1, 32, 49, 73). Additional features of fast-growing tumors include the presence of Antoni B tissues containing extratumoral or intratumoral cystic components, the over-expression or amplification of G1 regulators of the cell cycle such as cyclin D1 and cyclin D3, and the expression of erbB2 and erbB3 membrane tyrosine kinases (16, 20, 24, 74). When examining risk factors that may increase the likelihood of tumor diagnosis, the only endogenous or exogenous factors associated with the features of fast-growing tumors are patient sex and repeated environmental insults to the vestibulocochlear nerve that may lead to chronic inflammation. Proinflammatory cytokines such as IL-6, IL-1β, and TNF-α may initiate an inflammatory response after loud noise exposure and thus may be involved in cochlear damage (75).

1.5 Clinical Presentation

Symptoms of acoustic neuroma are highly variable and include unilateral high-frequency sensorineural hearing loss, tinnitus, dysequilibrium, pressure in the ear, otalgia, and occasionally vertigo, which result from pressure exerted by the tumor upon the cochlear and vestibular portions of the eighth cranial nerve (2, 6, 12). Approximately 10 percent of cases of unilateral progressive hearing loss are caused by acoustic neuromas (1). Hearing loss is the most common finding in patients with acoustic neuromas, with
more than 95 percent of patients experiencing this symptom over the course of their disease (2, 5). The mechanism of hearing loss is cochlear nerve compression (2). This symptom may be of several years’ duration prior to diagnosis (37, 49). Alternative explanations for hearing loss and tinnitus are made in the majority of acoustic neuroma cases, resulting in diagnostic delay due to the patient or due to the physician (50). Diagnostic delay is the period between the appearance of the first symptom and the time that first medical attention is sought. The average time from onset of symptoms to clinical diagnosis has been shown to range from approximately 4 to 7.3 years (12, 27, 37).

Nevertheless, as many as 5 to 12 percent of patients with newly diagnosed acoustic neuromas have normal hearing, in part as a result of the detection of smaller tumors by means of MRI (2, 49). In most cases, the onset of hearing loss is gradual, but in 5 to 15 percent of cases it may be sudden if compression of the internal auditory artery occurs (1, 2, 5). Another consequence of cochlear nerve dysfunction is tinnitus, usually presenting with concomitant hearing loss (2, 5). Dysequilibrium and vertigo are vestibular symptoms present in approximately 50 percent of patients (2). Ironically, vestibular symptoms tend to be late in the course of the disease and mild in nature, despite the predominant origin of acoustic neuromas on the vestibular division of the eighth cranial nerve (1).

Symptoms related to any intracranial mass lesion may also be present. These include sensory changes on the face or tongue, decreased corneal reflex, direction-changing nystagmus, ipsilateral numbness of the face, facial nerve motor dysfunction, a slurring of speech, ataxia, gait disturbance, an incoordination of one or both upper
extremities, numbness or tingling of the malar eminence, and occasionally long tract signs (1, 2, 6). Facial nerve dysfunction generally occurs late in the course of the disease and is rarely associated with small tumors (2). Decreased or absent corneal reflex is a consequence of trigeminal nerve dysfunction, although this deficit is rarely noticed by patients (2). Trigeminal nerve dysfunction is, however, responsible for the more common complaint of numbness or tingling of the malar eminence (2). Brainstem compressive symptoms include ipsilateral upper or lower extremity dysfunction and cerebellar symptoms include ataxia and gait disturbance (2). These symptoms occur very late in the disease and are observed with very large tumors (2).

Raised intracranial pressure, headaches, nausea, vomiting, obtundation, papilloedema, and dullness of mental faculties are gradual and persistent symptoms characteristic of the later stage of the disease (2, 6). These symptoms appear gradually and are persistent (2). The appearance of headache as a symptom of an acoustic neuroma is typically a sequela of hydrocephalus (2).

In summary, the symptoms of acoustic neuromas are highly dependent on tumor size (1). Most patients with small tumors present with unilateral hearing loss, tinnitus, and symptoms of vestibular nerve compression (2). Patients with larger tumors present with symptoms of trigeminal nerve dysfunction, facial nerve dysfunction, and symptoms related to increased intracranial pressure (2). Finally, continued growth of the tumor often results in symptoms related to brainstem and cerebellar compression (2).
1.6 Diagnostic Modalities

Only 5 percent of patients presenting with symptoms suspicious for acoustic neuroma will in fact have the tumor (1). The primary diagnostic modalities for acoustic neuromas are audiometric assessment and imaging assessment (2, 5). Audiometry is a sensitive, nonspecific method of screening for acoustic neuromas and should include puretone air and bone conduction thresholds, speech reception thresholds, and speech discrimination scores (1, 51). Asymmetric high-frequency sensorineural hearing loss is demonstrated in the majority of patients with acoustic neuromas who undergo audiograms (1, 2). High frequency hearing loss is attributable to the compression by the tumor of those cochlear nerve fibers arranged in the outer part of the nerve (1). Loss of speech discrimination is also associated with acoustic neuromas (1, 2). However, it is important to note that a normal audiogram does not rule out acoustic neuroma, as 12 percent of patients with acoustic neuromas may have normal audiograms (2, 12).

On physical exam spontaneous nystagmus may be evidence of vestibular dysfunction (2). When present, the nystagmus is usually horizontal (2). Vestibular testing, such as electronystagmography is a quantitative method of assessing spontaneous and induced nystagmus using periorbital electrodes to detect the electrical field shifts caused by the moving eye (1). However, it has shown to be inconsistent in its ability to diagnose acoustic neuromas and it is not cost effective (2). The sensitivity of electronystagmography is 78-98%, whereas the specificity is very poor (1). The diagnostic value of vestibular testing is thought to be inferior to that of audiometry, as the
vestibular system has a good compensatory ability in the presence of an acoustic neuroma tumor (52). Consequently, the role of vestibular tests in the diagnostic work-up for acoustic neuromas continues to diminish (2, 49).

The auditory brainstem response which records the passage of electrical events in the eighth nerve and brainstem following a sound stimulus, is the most reliable and reproducible audiometric testing available for detecting acoustic neuromas (1, 4, 5). An advantage of auditory brainstem response testing over electronystagmography is its lower cost (52). This test replaced older traditional audiological tests such as speech audiometry, stapedial reflex audiometry, loudness balance, and Carhart’s tone decay test (5). Auditory brainstem response has high sensitivity of up to 93-100%, but its specificity is somewhat lower (1, 2, 5). The sensitivity of auditory brainstem response makes it very practical for ruling out acoustic tumors when a negative result is found (1). However, its ability to detect small acoustic neuromas is limited and auditory evoked responses may not be possible if severe hearing loss is present (2, 52).

The diagnosis of acoustic neuromas has been revolutionized by the introduction of MRI with gadolinium enhancement, which remains the most sensitive diagnostic method for detecting small acoustic neuromas (2, 5). It is particularly useful in its ability to detect intracanalicular tumors (49). In addition, MR imaging exhibits exceptional soft tissue visualization, but it does not show bony details (2). The gadolinium enhancement allows a small tumor surrounded by bone to be seen as a bright signal bordered by a black background (2). This technique is able to detect very small tumors, with a very low false-positive rate, and is considered the gold standard for the detection of acoustic
tumors (2, 5). In addition, both sides of the head can be imaged at the same time (5). The disincentive to the use of MRI as a screening tool for acoustic neuromas is its higher cost (52).

If MRI facilities are not available, computed axial tomography (CT) scanning is the next best approach, although its role is limited in detecting small acoustic neuromas due to insufficient soft tissue differentiation and resolution (2, 5). CT scanning will consistently miss tumors smaller than 15 mm, limiting its value as an effective screening tool for acoustic neuromas (1).

In general, single tests are diagnostically inefficient for the diagnosis of acoustic neuromas because of the unacceptable level of false-negative results, false-positive results, or both that occur (53). The decision as to which test to use is dependent on level of suspicion, as well as clinical judgment (52). Specific factors involved in the decision are family history, asymmetry of auditory symptoms, brainstem evaluation findings, and symptoms consistent with NF2 (52).

1.7 Management

The optimal treatment for a patient with an acoustic neuroma is total excision of the tumor in a single surgical procedure with minimal morbidity and mortality, combined with preservation of neurologic function (52). If a patient is not a candidate for total surgical excision then other management options include observation, subtotal surgical excision, and various types of radiation therapy, including stereotactic radiotherapy (52). The decision as to whether and when a patient should be treated remains a complex issue. Younger patients with evidence of tumor growth or with progressive neurologic
symptoms are clearly candidates for surgical intervention (52). Conversely, elderly patients without evidence of tumor growth or severe neurologic deficits may be best served by long-term observation (52). In addition, patients with very small, asymptomatic acoustic neuromas identified by MRI with contrast enhancement may also be good candidates for observation (12, 52).

Observation, also known as radiologic surveillance, is a mode of conservative management involving the serial assessment of tumor growth by radiologic imaging, in conjunction with periodic clinical assessment of symptom progression (39). The major assumption with radiologic surveillance is that the majority of acoustic neuromas will not grow and that immediate surgical or radiological intervention poses a greater risk of complications to the patient than the potential outcome of delayed intervention (39). This management option is chosen by some patients due to advanced age, poor medical condition, or fear of surgery (49).

Specific preoperative findings have been identified to help predict postoperative outcome (52). For example, a patient with mild hearing loss and normal auditory brainstem response test who undergoes surgical excision of a tumor is more likely to experience hearing preservation than a patient with a tumor larger than 20 mm or with a tumor that fills the fundus of the internal auditory canal (52). The three major surgical approaches for total removal of an acoustic neuroma tumor are each characterized by advantages and disadvantages (49, 52). The middle fossa approach is suitable for small tumors limited to the internal auditory canal and provides increased probability for hearing preservation, whereas it is not suitable for larger tumors (12, 52). The translabyrinthine approach does not facilitate hearing preservation, however it does allow
facial nerve preservation during the removal of small and large tumors (12, 52). Finally, the suboccipital or retrosigmoid approach is suitable for small or large tumors and allows identification of the brain stem, cranial nerves, and cerebral vasculature (12, 52). This approach facilitates hearing preservation in patients with small tumors (52).

Total tumor removal is accomplished in the majority of cases and genuine tumor recurrence is rare (5). The results of surgical excision of an acoustic neuroma are predominantly dependent on the tumor size and the skill and experience of the surgical team (5). The surgical management of acoustic neuromas is also enhanced by intraoperative real-time neurologic monitoring (5, 52). This includes the preservation of facial nerve function, as well as the use of intraoperative auditory brainstem response monitoring (12, 52). Hearing preservation has been reported to be more successful in tumors smaller than 20 mm in diameter (49).

Patients unable or unwilling to undergo surgical excision of a tumor may be candidates for radiotherapy (12, 52). Options for radiotherapy include conventional photon beam therapy, particle beam therapy, or stereotactic radiotherapy (52). The latter treatment uses multisource cobalt 60 units for single-dose, external gamma ray therapy and retardation of tumor growth has been observed in the majority of patients treated with this type of radiotherapy (12, 52). In 45 percent of patients treated with stereotactic radiotherapy tumor shrinkage is achieved (12, 52). An important component of management is patient follow-up whereby repeated neurologic examination, audiologic assessment, and radiographic imaging are performed every 3 to 6 months initially to every 1 to 2 years, depending on the patient’s clinical course (35, 52).
Finally, chemotherapy has been reported in the treatment of patients with bilateral acoustic neuromas (49). One report of a chemotherapeutic treatment regimen included the use of cyclophosphamide, doxorubicin, and dacarbazine (49). However, surgical and radiotherapeutic intervention remain the primary treatment modalities in use today.

1.8 Incidence, Age and Sex Distribution

The true incidence of acoustic neuromas has been difficult to estimate (2, 4). The incidence has been reported to range from 1 to 20 per million per year (3, 4, 54). In studies of temporal bone materials, undiagnosed acoustic neuromas were found in 0.57-2.7% of the bones studied (33, 34). A study of acoustic neuromas in a review of 24,000 brain MRIs reported a prevalence of 0.07% (2). When comparing the clinical incidence of acoustic neuromas to the prevalence of occult acoustic neuromas ascertained from histopathological studies of temporal bones, it can be concluded that the vast majority of tumors that exist are never clinically manifested (33, 53).

Acoustic neuromas are most commonly diagnosed between the ages of 30 and 68 (1, 35). Reported cases of acoustic neuroma occurring in childhood are rare and in such patients other evidence of NF2 should be investigated (1, 9). In the study of 146 cases of acoustic neuroma presented in Chapter 2 the median age of the cases was 52 years (55). In the second study of 793 cases of acoustic neuroma presented in Chapter 3 the median age of the cases was 54 years.

The sex ratio (females/males) for acoustic neuromas has been reported to be >1 (3, 5, 12, 56). However, data from the Central Brain Tumor Registry of the United States (CBTRUS) do not support a female/male difference (57). Nevertheless, the studies
presented in Chapters 2 and 3 analyze Swedish data and the sex ratio (females/males) of acoustic neuromas in the Nordic counties has been shown to be >1. This sex ratio may indicate that hormones play a role in the etiology of acoustic neuromas (3, 58). Little is reported in the literature regarding acoustic neuromas and ethnic distribution. The tumor has been reported to be higher in whites than in non-whites (57) as well as being uncommon in individuals of African ancestry (5).

According to some studies the incidence of acoustic neuromas has been increasing (3, 54, 57). This may be due to several factors. Steady improvements in diagnosis, such as the introduction of auditory brainstem response, CT, and MRI could explain part of the increased incidence (3, 57). Increased awareness among physicians and patients of the symptoms of acoustic neuromas may have caused an increase in the reporting of the tumor (3, 54). Changes in classification or coding may also explain some of the trend, whereby registries may have misclassified nonvestibular schwannomas as acoustic neuromas (3, 57). Or, there may be a true increase in the incidence of these tumors (57). The trend may also lend support to the emerging hypotheses regarding an environmental cause of these tumors. Established and hypothesized risk factors have been reported extensively in the literature and include ionizing radiation exposure, cellular telephone use, specific occupations, a possible hormonal cause, and loud noise exposure.

1.9 Risk Factors

The causes of acoustic neuromas are largely unknown. Relatively few studies have addressed this specific tumor type, as acoustic neuromas are seldom analyzed separately in risk factor analyses and are more often grouped under the general heading
of brain tumors (59). The current epidemiologic literature on brain tumors is largely concerned with risk of glioma or risk of brain tumors in general (60). Ionizing radiation exposure is the only well-established exogenous risk factor for acoustic neuroma and has been confirmed in studies of radiation treatments and dental X-rays (61, 62). Individuals who underwent radiation treatment of tinea capitis during childhood were found to develop an excess of benign and malignant brain tumors of various histological types, including acoustic neuromas (55, 62). In addition, a study of atomic bomb survivors found that the intracranial tumor subtype most strongly related to ionizing radiation exposure was acoustic neuroma (61, 62). A statistically significant dose-related excess of nervous system tumors, including schwannomas was observed in the cohort of atomic bomb survivors (61). The excess relative risk per sievert (Sv) of absorbed dose for schwannomas was 4.5 (95 percent confidence interval: 1.9, 9.2) and the dose-response relationship was linear (61). Exposure to even moderate doses (i.e. <1 Sv) of radiation was associated with an elevated incidence of nervous system tumors, including schwannomas (61).

The association between the non-ionizing radiation from cellular telephones and the risk of acoustic neuroma has been examined in several studies. However, the evidence of an association so far is limited (63-70). This tumor is of particular interest in relation to cellular telephones because the radiofrequency radiation emitted during transmission is absorbed within a small area of the head close to the handset, which includes the vestibular division of the eighth cranial nerve where the majority of acoustic neuromas develop (64, 66). There is general agreement that the heating of brain tissue by radiofrequency radiation from cellular telephones is negligible and that any
cancerogenic effect would have to be mediated through a nonthermal mechanism (63, 69). In contrast to ionizing radiation, radiofrequency fields do not have enough energy to break chemical bonds or to cause DNA damage (66).

Of ten published studies to date examining cellular telephones and risk of acoustic neuroma, three showed any significantly increased risks (66, 67). A study performed by Hardell et al. showed an increased risk with use of analogue phones, with an odds ratio of 4.4 (95 percent confidence interval: 2.1, 9.2) for both ipsilateral and contralateral use (66, 69). This increased risk was observed in short-term users, however, the study has been heavily criticized for methodological and analytical limitations (64, 66). The second study performed by Lönn et al. reported a relative risk associated with cellular telephone use of at least 10 years’ duration to be 1.9 (95 percent confidence interval: 0.9, 4.1). When the analysis was restricted to tumors on the same side of the head as the telephone was normally used, the relative risk increased to 3.9 (95 percent confidence interval: 1.6, 9.5) (64, 66). In the study no increased risk was observed for short-term cellular telephone use and a short latency period, regardless of tumor or cellular telephone laterality (64). Finally, the third pooled study of two case-control studies conducted by Hardell et al. demonstrated significantly increased risk of acoustic neuromas for analogue cellular telephones, digital cellular telephones, and cordless telephones (70). The highest risk was found for analogue cellular telephone use with a latency period of >15 years with an odds ratio of 3.8 (95 percent confidence interval: 1.4, 10) (70).

The seven published studies that showed no increased risk were small and had few long-term users (64, 66, 67). Results of these studies pertain primarily to analogue telephones which became widely used in the mid-1990s. It is important to note that the
effects of digital telephones are difficult to separate from that of analogue telephones because almost all analogue users are also users of digital telephones (64). One study that found an increased risk of acoustic neuromas with more than 10 years of analogue telephone use did not, however, find an increased risk with digital telephone use (64). Studies of ionizing radiation have shown that the induction period of radiation-induced solid tumors is likely to be at least 10 years, therefore, a carcinogenic effect following a long induction period would remain undetected at the current time (64).

Elevated risk of acoustic neuromas has been associated with specific occupations such as truck drivers, gas station attendants, sales representatives, and teachers (60, 71). However, it remains unclear what specific environmental exposure within those occupations is responsible for the increased risk.

As mentioned previously, the sex ratio (females/males) for acoustic neuroma is >1 which suggests a possible hormonal cause (3, 58). In a study of brain tumors and menopausal status, menopausal women had a greatly reduced risk of developing meningiomas (odds ratio = 0.58, 95 percent confidence interval: 0.18, 1.90), but a greater risk of developing gliomas or acoustic neuromas (relative risk = 1.77, 95 percent confidence interval: 0.67, 4.68) (58). The reduction in risk for meningiomas may be attributable to the decreased estrogen levels during menopause, which is compatible with the previous finding that certain brain tumors have been found to increase in size during pregnancy, when estrogen levels are elevated (10, 58, 72). The study does not provide a hypothesis for the increased risk of acoustic neuromas during menopause, although the
authors do suggest that since males are at lower risk for developing acoustic neuromas than females, it is possible that the relative elevation of androgen levels after menopause is providing a protective effect (58).

Exposure to loud noise has been suggested as a potential risk factor for acoustic neuromas in two studies (55, 71). The first study by Preston-Matin et al. (1989) included 86 men in Los Angeles County aged 25-69 years, diagnosed with acoustic neuroma between 1978 and 1985. The cases were pair-matched to neighborhood controls. Study participants reported past loud noise exposures, and in addition self-reported occupational histories were reviewed by an occupational hygienist to determine whether or not significant noise exposure occurred. Loud noise was classified as either impact noise or continuous noise. In the study the odds ratio for ever having a job involving exposure to extremely loud noise was 2.2 (95 percent confidence interval: 1.12, 4.67). The study also found a dose-response effect for years of employment in an occupation with loud noise exposure ($P$ for trend = 0.02). More cases reported exposure to extremely loud noise on jobs held 10 or more years before the year of diagnosis with an odds ratio of 3.0 ($P=0.004$). The OR for exposure for 20 or more years during the period 10 or more years before diagnosis was 13.2 (95 percent CI: 2.01, 86.98). Two significant weaknesses of this study were that it included only men and it was not possible to report findings for nonoccupational loud noise exposure, as too few study participants reported such exposure. Recall bias is a potential problem in this study, as the study participants responded to a questionnaire inquiring about loud noise and other environmental exposures. The study did propose a hypothesis that mechanical trauma may contribute to acoustic neuroma tumorigenesis (71).
A similar hypothesis was proposed in a subsequent study by Edwards et al. (2006) examining loud noise exposure in 146 acoustic neuroma cases diagnosed between 1999 and 2002 in Sweden. Given the findings of the earlier study of loud noise and acoustic neuromas, the goal of the second study was to further examine the role of loud noise in acoustic neuroma etiology. The population-based case-control study of both sexes compared reports on type and duration of occupational and non-occupational loud noise exposure. Controls were selected randomly from the study base and were frequency matched on age, sex and residential area. Those reporting occupational loud noise exposure were at increased risk for acoustic neuromas with an odds ratio of 1.43 (95 percent confidence interval: 0.96, 2.13). Exposure to nonoccupational loud noise also increased the risk for acoustic neuromas (odds ratio = 1.38, 95 percent confidence interval: 0.80, 2.36). Individuals reporting loud noise exposure from any source were found to be at increased risk for acoustic neuromas with an odds ratio of 1.55 (95% confidence interval: 1.04, 2.30). Also of interest were those study participants exposed to loud noise with hearing protection. The odds ratio for those individuals was 0.92 (95 percent confidence interval: 0.51, 1.64) (55).

In the study by Edwards et al. the risk of acoustic neuromas was also examined according to duration of loud noise exposure. A dose-response effect was evident with increasing years of loud noise exposure ($P$ for trend = 0.0056). In an analysis of loud noise exposure type, exposure to loud noise from machines, power tools and/or construction increased the risk for acoustic neuromas (odds ratio = 1.79, 95% confidence interval: 1.11, 2.89), as did exposure to loud music (odds ratio = 2.25, 95% confidence interval: 1.20, 4.23). Finally, the significance of latency period and the risk of acoustic
neuromas was evaluated. The odds ratio for a latency period of ≥13 years since first loud noise exposure from any source was 2.12 (95% confidence interval: 1.40, 3.20). The findings of an increased risk of acoustic neuromas with loud noise exposure in the second study supported the previous research. However, further research was recommended in order to validate self-reports of loud noise exposure (55).

A third study of objectively measured occupational noise and the risk of acoustic neuromas was conducted in a large cancer registry based case-control study. The study was conducted in order to facilitate further examination of the role of loud noise in acoustic neuroma etiology. A total of 793 acoustic neuroma cases aged 21-84 years were identified between 1987 and 1999 from the Swedish Cancer Registry. The 101,756 controls randomly selected from the study base were frequency matched to cases on age, sex, and calendar year of diagnosis. Occupational information, available for 599 of the cases and 73,432 of the controls, was obtained from censuses and linked to a job exposure matrix based on actual noise measurements. Contrary to previous study results, all risk estimates were close to unity, regardless of noise exposure level or parameter. The overall odds ratio for exposure to ≥85 decibels of noise was 0.89 (95 percent confidence interval: 0.64, 1.23). Risk estimates for occupational noise exposure with a 5 year, 10 year, and 15 year latency period were all close to unity and all of the CIs for the three latency periods for both low and high noise included the null. Odds ratios for exposure to occupational noise according to one, two, three, or four consecutive censuses closest in time prior to reference year were all slightly above unity but all of the corresponding CIs included the null. The overall results of the study did not support the hypothesis that
occupational noise exposure is a risk factor for acoustic neuromas and the effect of non-differential misclassification of exposure must be considered as a potential cause of the negative findings.

2.10 References


CHAPTER 2

EXPOSURE TO LOUD NOISE AND RISK OF ACOUSTIC NEUROMA

2.1 Abstract

Exposure to occupational loud noise has been previously identified as a possible risk factor for acoustic neuroma in only one relatively small (n=86 cases) case-control study of men. The goal of the present study was to further examine the role of loud noise in acoustic neuroma etiology. In our population-based case-control study of both sexes conducted from 1999-2002 in Sweden, I compared reports on type and duration of occupational and non-occupational loud noise exposure of 146 acoustic neuroma cases and 564 controls. Controls were randomly selected from the study base and were frequency matched on age, sex and residential area. I found that individuals reporting loud noise exposure from any source were at increased risk for acoustic neuroma (odds ratio (OR) = 1.55, 95% confidence interval (CI): 1.04, 2.30). Exposure to loud noise from machines, power tools and/or construction increased the risk for acoustic neuroma

as did exposure to loud music (OR = 2.25, 95% CI: 1.20, 4.23). The OR for a latency period of ≥13 years since first loud noise exposure from any source was 2.12 (95% CI: 1.40, 3.20). The findings of an increased risk of acoustic neuroma with loud noise exposure support previous research.

2.2 Introduction

Acoustic neuroma, also referred to as vestibular schwannoma, is a benign tumor of the vestibular division of the eighth cranial nerve (1, 2). This tumor results in hearing loss, tinnitus and dysequilibrium (3, 4). The tumor constitutes from 6-10 percent of all intracranial tumors, with an incidence of 1-20 per million per year (5-7). The sex ratio (females/males) for acoustic neuroma has been reported to be >1 (1, 6, 8, 9) and the tumor occurs mainly in individuals aged 50 years or older (6). Acoustic neuromas present clinically as two distinct types, the bilateral hereditary type and the unilateral sporadic type (4, 8). In the present study we examine unilateral acoustic neuroma which comprises 90-95 percent of all acoustic neuromas (6, 10).

We report the results from the Swedish portion of the INTERPHONE study, an international collaborative case-control study of brain tumors, acoustic neuroma, and parotid gland tumors in relation to mobile phone use and other potential risk factors (11). In a recent publication from this study, an association between acoustic neuroma and mobile phone use was reported that is awaiting confirmation from other studies (12). In the present study we focus instead on another potential acoustic neuroma risk factor, loud noise exposure. The only available study to date examining loud noise exposure and
acoustic neuroma risk was limited by the relatively small number of acoustic neuroma cases available for inclusion in the analysis, as well as the restriction of the study population to men (13).

2.3 Materials and Methods

2.3.1 Study design and population  A population based case-control study was conducted including all individuals aged 20 to 69 years who resided in three geographical regions covered by the regional cancer registries in Stockholm, Göteborg, and Lund, Sweden, which comprised a population of approximately 3.1 million people. Data were collected during the period 1999-2002. Study approval was obtained from the institutional Ethics Committee and oral informed consent was obtained from all study participants.

2.3.2 Acoustic neuroma case ascertainment  Eligible cases were all patients diagnosed with acoustic neuroma (ICD-10 C72.4 and ICD-O-2 9560.0) during the period from 1st of September 1999 to 31st of August 2002 in the areas covered by the Lund and Göteborg Cancer Registries and from 1st of January 2000 to 31st of August 2002 in the Stockholm Cancer Registry area. Continuous identification of cases throughout the study period was achieved through collaboration with neurosurgery, oncology, neurology, and otorhinolaryngology clinics at hospitals within the geographical regions covered by the study. Any patients missed during weekly visits to these clinics were subsequently identified during quarterly regional Cancer Registry searches. The first medical examination resulting in diagnosis of acoustic neuroma was used as the date of diagnosis and also as the reference date for exposure calculations.
Medical records for all cases were examined to confirm the diagnosis and to determine the side of the head on which the tumor was located. Histopathological reports were used to verify diagnosis in 58 cases (40%) and the remaining cases were diagnosed by computerized axial tomography or magnetic resonance imaging. Histological classification of the cases as acoustic neuroma was performed by pathologists at the hospitals in the three study regions where the cases underwent surgery or biopsy. We identified a total of 160 eligible acoustic neuroma case patients, of whom 146 (91 percent) were interviewed. Those cases who did not participate included 11 (7 percent) who would not consent to the study and three (2 percent) who could not be contacted.

2.3.3 Controls Controls were randomly selected approximately every 2 months from the continuously updated Swedish population registry. The number of controls required for each case was stipulated by the common protocol of the INTERPHONE study (one per brain tumor case, two per acoustic neuroma case, and three per parotid gland tumor case). Of the 838 controls identified for inclusion in the study, 564 (67 percent) were interviewed. Those controls who did not participate included 127 (15 percent) who would not consent to the study and 147 (18 percent) who could not be reached by phone in order to make an appointment for an interview. There were no major differences between the respondents and the non-respondents with regard to age, sex and area of residence. For controls, the reference date was defined as the date of identification of the control, adjusted for the average time difference between the date of diagnosis and the date of identification of the cases within the same matching stratum. This assured a comparable length of follow-up for cases and controls.
2.3.4 Data collection and loud noise exposure assessment

Identification of cases and controls occurred prospectively from September 2000 through August 2002, and retrospectively in the 12 months prior to September 2000 in the Lund and Göteborg study regions and in the 8 months prior September 2000 in the Stockholm study region. The study participant contact and interview procedures were similar for cases and controls. Interviews were conducted by study nurses or the study neuro-psychologist using laptop computers. Study participants who would not participate in a personal interview were offered a telephone interview. Those who refused participation in any kind of interview were offered the option of completing a short written questionnaire instead. The written questionnaire was focused on mobile phone use and did not include questions about loud noise. Therefore, participation rates are lower in the analyses reported here compared to the analysis of mobile phone use described earlier (12). A proxy respondent was used in two cases where the case had died before the first contact by study personnel. Eligibility criteria for both cases and controls required that they were not completely deaf prior to the reference date. One control was excluded for this reason. The cases and controls also had to possess the intellectual and language skills necessary to complete the interview. Three cases and 18 controls were excluded because they did not speak Swedish; four controls were excluded because of insufficient intellectual skills.

The study participants were asked if they were exposed to occupational loud noise and also if they were exposed to regular non-occupational loud noise. Exposure to loud noise was defined as a level of 85 dB or more. This cut-off was explained to the study participants by means of a diagram depicting a decibel scale and associated loud noise exposures. If they were exposed to either occupational loud noise, regular
non-occupational loud noise, or both, the study participants were then asked to specify
the activities in which they were exposed to loud noise and the year in which the
exposure started and the year in which it stopped. They were also asked if there were any
years during this period in which they were unexposed.

Total years of loud noise exposure were categorized into less than 5 years, 5-14
years and 15 years or more (with cut points at approximately the 25th and 75th percentile
for controls). In the analysis of type of loud noise exposure, the following categories were
created: (1) exposure to machines, power tools and/or construction; (2) exposure to
motors, including airplanes; (3) exposure to loud music, including employment in the
music industry; and (4) exposure to screaming children, sports events and/or restaurants
or bars. The remainder was classified as “other” types of loud noise exposure. Ninety-
seven percent of the loud noise exposure responses could be categorized into one of the
four loud noise exposure types. Data regarding the use of hearing protection were also
collected. This would allow us to determine if there was any difference between study
participants who were unexposed and participants who used hearing protection. Finally,
complete job history was collected for the 20 years preceding diagnosis, but not in
sufficient detail to be used as a loud noise exposure validation tool.

2.3.5 **Statistical analysis**   Unconditional logistic regression models adjusted
for age (5 year categories), sex and local cancer registry region were used to estimate
odds ratios (ORs) and their respective 95 percent confidence intervals (CIs) (PROC
LOGISTIC in SAS, version 8; SAS Institute, Inc., Cary, North Carolina) (14). The OR
was used as an estimate of the relative risk in the analysis of the interview data. In the
analysis of loud noise exposure type (Table 2.4), we also adjusted for highest level of
education which we used as a proxy for socio-economic status. In the evaluation of potential confounding variables, the data presented in Table 2.2 were stratified on ionizing radiation exposure due to medical treatment, as well as on mobile phone use. The odds ratios did not differ within the different strata, discounting these variables as potential confounders or effect modifiers. In addition, radiation exposure and mobile phone use were added to the logistic regression model. However, the changes in the ORs were negligible and therefore these variables were not included in the final model. Tests for trend were calculated using the Cochran-Armitage test for trend. All tests of statistical significance performed were two-sided.

2.4 Results

Basic demographic characteristics of cases and controls are presented in Table 2.1. The median age of the cases and controls was 52 years and 54 years, respectively. Tumor location was more common on the right side (59 percent) than on the left side (41 percent).

Study participants were initially classified as unexposed to loud noise or exposed to occupational and/or regular non-occupational loud noise, with either hearing protection or without hearing protection. Ten percent of the cases and 11 percent of the controls who were exposed to occupational loud noise, regular non-occupational loud noise, or both, reported using hearing protection most of the time.

The ORs for acoustic neuroma by loud noise exposure are shown in Table 2.2. The OR for occupational loud noise exposure (OR = 1.43, 95 percent CI: 0.96, 2.13) was similar to the OR for regular non-occupational loud noise exposure (OR = 1.38, 95
percent CI: 0.80, 2.36). When study participants exposed to occupational loud noise or regular non-occupational loud noise (or both) were combined, the OR increased to 1.55 (95 percent CI: 1.04, 2.30). The OR for the group exposed to loud noise with hearing protection was 0.92, 95 percent CI: 0.51, 1.64. In all subsequent analyses the subjects using hearing protection were categorized as unexposed to loud noise. In an additional analysis, those study participants using hearing protection were excluded. There was a slight rise in the odds ratios for the three loud noise exposure categories listed in Table 2.2. Finally, the overall analysis presented in Table 2.2 was stratified on hearing loss. The patterns within the hearing loss and the no hearing loss groups were found to be comparable.

Table 2.3 displays results according to duration of loud noise exposure, combining occupational and regular non-occupational loud noise. For males and females combined, all of the exposure duration groups had elevated ORs, with the highest OR at 1.64 (95 percent CI: 0.91, 2.91) for the group with 5-14 years of loud noise exposure. A dose-response effect is evident with increasing years of loud noise exposure ($P$ for trend = 0.0056). When the loud noise exposure duration data were analyzed separately for males and females, the highest OR for males was 2.12 (95 percent CI: 0.99, 4.57) for 5-14 years of loud noise exposure and the highest OR for females was 3.34 (95 percent CI: 1.32, 8.43) for $\geq$15 years of loud noise exposure. An additional analysis of loud noise exposure duration was performed, excluding the five years prior to diagnosis. However, the pattern in the additional analysis was similar to that of the original analysis. Finally, the duration of exposure analysis was repeated, dropping hearing protection from the
comparison group. There were negligible changes in the odds ratios for the analysis of
the male study participants, the female study participants and the combined group.

Table 2.4 presents type of loud noise exposure grouped into four distinct
categories. A significantly greater proportion of men than women were exposed to
machines, power tools and construction, as well as to motors, including airplanes. A
greater proportion of men were exposed to loud music, including employment in the
music industry and a greater proportion of women were exposed to screaming children,
sports events and/or restaurants/bars, although the latter differences were not significant.
All of the categories had elevated ORs. The two categories with the highest ORs were
exposure to machines, power tools and/or construction, with an OR of 1.79 (95 percent
CI: 1.11, 2.89) and exposure to music, including employment in the music industry with
an OR of 2.25 (95 percent CI: 1.20, 4.23). Subgroup logistic regression analyses were
performed for males and females separately. The resulting ORs were in the same
direction for both subgroups, although the numbers of study participants in each
subgroup were too small for meaningful analysis and are therefore not presented.

To evaluate the significance of latency period and the risk of acoustic neuroma we
analyzed the data using three latency periods. The data were analyzed for those study
participants with <13 years, 13-26 years, and ≥27 years since first regular loud noise
exposure (with cut points at approximately the 25th and 75th percentile for controls). The
data are presented in Table 2.5 for occupational and/or regular non-occupational loud
noise exposure only, as the numbers of study participants in the analyses of other
categories of loud noise exposure were too small for meaningful analysis. The OR
increased with increasing latency period ($P$ for trend = 0.0029). The OR for ≥13 years
since first regular loud noise exposure was 2.12 (95% CI: 1.40, 3.20) (data not shown).

An additional analysis of latency period was performed, excluding the five years prior to diagnosis. However, the pattern in the additional analysis was similar to that of the original analysis.
Table 2.1. Selected characteristics of the 710 study participants, Sweden, 1999-2002.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=146)</th>
<th>Controls (n=564)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>77</td>
<td>53</td>
</tr>
<tr>
<td>Female</td>
<td>69</td>
<td>47</td>
</tr>
<tr>
<td><strong>Age at reference date (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>40-49</td>
<td>27</td>
<td>19</td>
</tr>
<tr>
<td>50-59</td>
<td>57</td>
<td>39</td>
</tr>
<tr>
<td>60-69</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td><strong>Highest Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsory school</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Vocational/secondary school</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Upper secondary school</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>University</td>
<td>53</td>
<td>36</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
43

<table>
<thead>
<tr>
<th>Exposure to loud noise</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never&lt;sup&gt;3&lt;/sup&gt;</td>
<td>72</td>
<td>340</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>With hearing protection</td>
<td>15</td>
<td>61</td>
<td>0.92</td>
<td>0.51, 1.64</td>
</tr>
<tr>
<td>Occupational</td>
<td>64</td>
<td>195</td>
<td>1.43</td>
<td>0.96, 2.13</td>
</tr>
<tr>
<td>Non-occupational</td>
<td>27</td>
<td>77</td>
<td>1.38</td>
<td>0.80, 2.36</td>
</tr>
<tr>
<td>Occupational and/or non-occupational&lt;sup&gt;4&lt;/sup&gt;</td>
<td>74</td>
<td>223</td>
<td>1.55</td>
<td>1.04, 2.30</td>
</tr>
</tbody>
</table>

<sup>1</sup> OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex and region
<sup>2</sup> CI, confidence interval
<sup>3</sup> Reference category includes individuals never exposed to loud noise
<sup>4</sup> Exposure to occupational loud noise, or non-occupational loud noise, or both occupational and non-occupational loud noise

Table 2.2. Odds ratios for acoustic neuroma according to loud noise exposure, Sweden, 1999-2002.
## Table 2.3. Odds ratios for acoustic neuroma according to duration of loud noise exposure, Sweden, 1999-2002.

<table>
<thead>
<tr>
<th>Males and females</th>
<th>Cases</th>
<th>Controls</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
<th>P for trend(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of exposure to loud noise</td>
<td>No.</td>
<td>%</td>
<td>No.(^3)</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Never or used hearing protection</td>
<td>87</td>
<td>60</td>
<td>401</td>
<td>71</td>
<td>1.00</td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>14</td>
<td>10</td>
<td>38</td>
<td>7</td>
<td>1.51</td>
</tr>
<tr>
<td>5-14 years</td>
<td>20</td>
<td>14</td>
<td>51</td>
<td>9</td>
<td>1.64</td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>25</td>
<td>17</td>
<td>64</td>
<td>11</td>
<td>1.56</td>
</tr>
</tbody>
</table>

### Males

<table>
<thead>
<tr>
<th>Years of exposure to loud noise</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
<th>P for trend(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or used hearing protection</td>
<td>40</td>
<td>52</td>
<td>177</td>
<td>65</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>8</td>
<td>10</td>
<td>18</td>
<td>7</td>
<td>1.71</td>
<td>0.67, 4.38</td>
<td></td>
</tr>
<tr>
<td>5-14 years</td>
<td>14</td>
<td>18</td>
<td>27</td>
<td>10</td>
<td>2.12</td>
<td>0.99, 4.57</td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>15</td>
<td>19</td>
<td>48</td>
<td>18</td>
<td>1.18</td>
<td>0.60, 2.32</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### Females

<table>
<thead>
<tr>
<th>Years of exposure to loud noise</th>
<th>No.</th>
<th>%</th>
<th>No.</th>
<th>%</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
<th>P for trend(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or used hearing protection</td>
<td>47</td>
<td>68</td>
<td>224</td>
<td>77</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5 years</td>
<td>6</td>
<td>9</td>
<td>20</td>
<td>7</td>
<td>1.24</td>
<td>0.44, 3.52</td>
<td></td>
</tr>
<tr>
<td>5-14 years</td>
<td>6</td>
<td>9</td>
<td>24</td>
<td>8</td>
<td>1.01</td>
<td>0.36, 2.81</td>
<td></td>
</tr>
<tr>
<td>≥ 15 years</td>
<td>10</td>
<td>14</td>
<td>16</td>
<td>6</td>
<td>3.34</td>
<td>1.32, 8.43</td>
<td>0.024</td>
</tr>
</tbody>
</table>

---

1. OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex and region
2. CI, confidence interval
3. 4 male controls and 6 female controls did not specify duration of loud noise exposure
4. Cochran-Armitage test for trend

Table 2.3. Odds ratios for acoustic neuroma according to duration of loud noise exposure, Sweden, 1999-2002.
Table 2.4. Odds ratios for acoustic neuroma according to loud noise exposure type, Sweden, 1999-2002.

<table>
<thead>
<tr>
<th>Exposure to occupational and regular non-occupational loud noise</th>
<th>Cases</th>
<th>Controls</th>
<th>OR(^1)</th>
<th>95% CI(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or used hearing protection</td>
<td>87</td>
<td>401</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Machines, power tools and/or construction</td>
<td>35</td>
<td>90</td>
<td>1.79</td>
<td>1.11, 2.89</td>
</tr>
<tr>
<td>Motors, including airplanes</td>
<td>12</td>
<td>34</td>
<td>1.30</td>
<td>0.63, 2.67</td>
</tr>
<tr>
<td>Music, including employment in the music industry</td>
<td>21</td>
<td>48</td>
<td>2.25</td>
<td>1.20, 4.23</td>
</tr>
<tr>
<td>Screaming children, sports events and/or restaurants/bars</td>
<td>7</td>
<td>23</td>
<td>1.40</td>
<td>0.56, 3.49</td>
</tr>
</tbody>
</table>

\(^1\) OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex, region and education

\(^2\) CI, confidence interval
Table 2.5. Odds ratios for acoustic neuroma according to loud noise exposure and latency period, Sweden, 1999-2002.

<table>
<thead>
<tr>
<th>Time since first regular loud noise exposure (years)</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never or used hearing protection</td>
<td>87</td>
<td>401</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>6</td>
<td>36</td>
<td>0.68</td>
<td>0.26, 1.77</td>
<td></td>
</tr>
<tr>
<td>13-26</td>
<td>30</td>
<td>78</td>
<td>1.74</td>
<td>1.06, 2.84</td>
<td></td>
</tr>
<tr>
<td>≥27</td>
<td>23</td>
<td>39</td>
<td>2.15</td>
<td>1.19, 3.86</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

1 OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex and region
2 CI, confidence interval
3 includes exposure to occupational and/or regular non-occupational loud noise
4 10 controls did not specify year in which loud noise began
5 Cochran-Armitage test for trend
2.5 Discussion

2.5.1 Loud noise exposure and risk of acoustic neuroma

Exposure to any loud noise, to occupational loud noise and to regular non-occupational loud noise were all associated with an increased risk of acoustic neuroma. Each of our three categories of loud noise exposure duration were associated with an increased risk of acoustic neuroma, with the highest risk of acoustic neuroma for study participants exposed to loud noise for a duration of 5-14 years. The two types of loud noise exposure with the highest risk of acoustic neuroma were exposure to loud noise from machines, power tools and/or construction and exposure to loud noise from music, including employment in the music industry.

The results of the present study are in agreement with the only other known study examining loud noise exposure and the risk of acoustic neuroma (13). The previous study reported results in 86 males, a slightly larger number than the 77 males in the present study. Not only was our study able to replicate the previous study’s findings in males, but perhaps more importantly an elevated risk of acoustic neuroma was also found in females. In the previous study, the OR for ever having a job involving exposure to extremely loud noise was 2.2 (95 percent CI: 1.12, 4.67). The study also found a dose-response effect for years of employment in an occupation with loud noise exposure ($P$ for trend = 0.02). The OR for exposure for 20 or more years during the period 10 or more years before diagnosis was 13.2 (95 percent CI: 2.01, 86.98). The previous study included only men and was not able to report findings for non-occupational loud noise exposure, as too few study participants reported such exposure.
In our study, elevated risk of acoustic neuroma was found with all loud noise exposure duration categories in males, which is consistent with the previous study (13) and elevated risk of acoustic neuroma was found with all of the loud noise exposure duration categories in females. No comparison can be made with the previous study for the latter group, as they did not collect data on occupational loud noise exposure among females. One recent study of occupation and risk of meningioma and acoustic neuroma found that those occupations associated with an increased risk of acoustic neuroma were not occupations with which one would expect an unusually high exposure to loud noise (60). However, the study was only able to estimate loud noise exposure indirectly, as no data on loud noise exposure were collected. Finally, in the present study tumor location was found to be more common on the right side than on the left side. Other data also indicate a similar uneven distribution with regard to tumor laterality (16).

2.5.2 Other risk factors

In a previous report from the Swedish INTERPHONE study of mobile phone use and the risk of acoustic neuroma, the relative risk associated with mobile phone use of at least 10 years’ duration was shown to be 1.9 (95 percent CI: 0.9, 4.1). When the analysis was restricted to tumors on the same side of the head as the phone was normally used, the relative risk increased to 3.9 (95 percent CI: 1.6, 9.5). The study had a larger number of exposed acoustic neuroma cases than any of six previous studies examining mobile phone use and thus was better powered to study the effects of long-term mobile phone use (12). The findings of this recent study will require confirmation in other studies. Mobile phone use was evaluated in the present study and was not found to be a confounding variable.
Ionizing radiation exposure is the only well-established exogenous risk factor for acoustic neuroma. It has been found to increase acoustic neuroma risk among individuals who underwent radiation treatment of tinea capitis during childhood and who developed an excess of benign and malignant brain tumors of various histological types, including acoustic neuroma, and among survivors of the atomic bombings in Japan (17, 18). Ionizing radiation exposure due to medical treatment was evaluated in the present study and was not found to be a confounding variable.

It has been suggested that female hormones may also increase acoustic neuroma risk, although the evidence for this association is suggestive rather than definitive (6, 19). One line of evidence suggesting that female hormones play a role in the etiology of acoustic neuroma is that the incidence is higher in women than in men (1, 6, 8, 9). A population-based case-control study of brain tumors, including acoustic neuroma, and menopausal status, found a tendency towards an increased risk of acoustic neuroma for menopausal women (19). It is suggested that this is perhaps due to the cessation of estrogen production after menopause or even perhaps due to a protective effect of the relative elevation of androgen levels after menopause.

2.5.3 Diagnostic delay The majority of acoustic neuroma tumors grow slowly (20, 21). In our study it is likely that many of the cases had the tumor for several years before a clinical diagnosis was made. Diagnostic delay is the period between the appearance of the first symptom and the time that first medical attention is sought. According to another study, the delay from the first symptom until diagnosis averaged more than 5 years (22). In these patients the diagnostic delay ranged from 2 to 30 years. Hence, it is very difficult to predict the growth rate and as a result the latency period of
acoustic neuroma. In our analysis, however, we did observe an increased risk of acoustic neuroma as the latency period was increased ($P$ for trend = 0.0029). An increased risk of acoustic neuroma was found only with a latency of at least 13 years between exposure and diagnosis. This is consistent with the hypothesis that for slow-growing tumors such as acoustic neuroma, one would expect a higher risk with a longer latency period and lower risk with a shorter latency period.

2.5.4 Acoustic trauma and tumorigenesis

The results of the present study support the hypothesis that acoustic trauma due to loud noise exposure contributes to tumorigenesis. Damage to the structures of the ear caused by intense sound exposure appears to be caused by similar mechanisms in all mammals (23). It has been reported previously that damage to cochlear hair cells produced by acoustic trauma stimulates mitotic replication of normally postmitotic cells in the chicken and quail (24, 25). The supporting cells or perhaps unidentified stem cells that replicate as a result of the acoustic trauma, do not divide in the absence of trauma (24). Experimental studies in rodents have demonstrated mechanical damage to the organ of Corti and surrounding tissue, including the eighth cranial nerve, as a result of intense impulse noise (26, 27). Oxidative DNA damage in the cochlea following intense noise exposure was observed in one experimental study of rodents (28). If cancer risk is proportional to the number of proliferating cells, as has been previously postulated (29), then it is plausible that a benign tumor such as acoustic neuroma may arise as a result of cochlear hair cell trauma. During the cellular repair process, cellular division results in DNA replication errors which may in turn lead to chromosomal changes essential for neoplastic transformation (13).
2.5.5 Recall and selection bias

The tendency for patients with a tumor to focus on the reasons that they may have developed the disease is a potential source of recall bias in our study. As our study is a case-control interview study and as many of the cases were exposed to loud noise for 5 or more years’ duration, we cannot exclude the possibility that recall bias occurred. In their search for exposure to a putative risk, the cases may have focused on occupational exposures, including exposure to loud noise. In addition, 91 percent of the cases in the study reported unilateral hearing loss at the time of the interview, which is the primary symptom seen in patients with acoustic neuroma. This may have made the cases more aware of past loud noise exposures prior to their diagnosis than the controls, of which only 29 percent reported hearing loss at the time of the interview.

In the present study there was higher participation rate in the cases than in the controls, which could have caused selection bias. If willingness to participate was higher among those controls exposed to loud noise, then the risk of acoustic neuroma would have been underestimated. However, such selection bias is unlikely, as the primary aim of the INTERPHONE study was the evaluation of mobile phone use as a possible risk factor for acoustic neuroma and other brain tumors, not the evaluation of loud noise exposure. In addition, cases with loud noise exposure and subsequent hearing impairment may have sought medical attention for their hearing impairment and as a result may have been diagnosed with acoustic neuroma. This may have resulted in earlier detection of acoustic neuroma. Such a scenario would be possible in the music industry for example, in which hearing impairment is likely to be more prevalent than in other occupations.
This possible detection bias may have caused an overestimation of the true effect of loud noise exposure and is an issue that warrants further investigation in future studies.

The standardized face-to-face interviews used in this study decreased the likelihood of recall bias and provided more reliable answers to detailed questions than self-administered questionnaires (30). Although the interviewers were not blinded as to case and control status, the potential for interviewer bias was minimized by the use of a standard set of questions read verbatim from the laptop computer by trained study personnel. Also, it has been reported that patients with acoustic neuroma do not generally have memory deficits and as a result this should not have affected the quality of our data (22).

2.5.6 Conclusion We conclude that our data support the hypothesis that loud noise exposure is a risk factor for acoustic neuroma. Further research is needed to validate self-reports of loud noise exposure and evaluate the effect of potential detection bias.

2.6 Acknowledgments

I acknowledge funding from the European Union Fifth Framework Program, “Quality of Life and Management of living Resources” (contract QLK4-CT-1999-01563), the Swedish Research Council, and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers’ Forum and GSM Association. Provision of funds to the INTERPHONE study investigators via the UICC was governed by agreements that guaranteed
INTERPHONE’s complete scientific independence. These agreements are publicly available at http://www.iarc.fr/ENG/Units/RCAd.html.

I wish to thank the regional Cancer Registries and the area hospital clinics for their collaboration. I also thank the research nurses for their skillful work.

2.7 References


3.1 Abstract

Two prior epidemiologic studies of occupational noise exposure based on self-report have suggested an association with acoustic neuroma. The goal of the present study was to further examine the association between noise exposure and acoustic neuroma using an objective measure of exposure in the form of a job exposure matrix. A total of 793 acoustic neuroma cases aged 21-84 years were identified between 1987 and 1999 from the Swedish Cancer Registry. The 101,756 controls randomly selected from the study base were frequency matched to cases on age, sex, and calendar year of diagnosis. Occupational information, available for 599 of the cases and 73,432 of the controls, was obtained from censuses and linked to a job exposure matrix based on actual noise measurements. All risk estimates were close to unity, regardless of noise exposure

level or parameter. The overall odds ratio for exposure to $\geq 85$ decibels of noise was 0.89 (95% confidence interval: 0.64, 1.23). Contrary to previous study results, the findings do not demonstrate an increased acoustic neuroma risk related to occupational noise exposure even allowing for a long latency period. The effect of non-differential misclassification of exposure must be considered as a potential cause of the negative findings.

3.2 Introduction

Acoustic neuroma, also referred to as vestibular schwannoma, constitutes from 6-10 percent of all intracranial tumors, with an incidence of 1-20 per million per year (1-3). The sex ratio (females/males) has been reported to be >1 (1, 4-6) and the tumor occurs mainly in individuals aged 50 years or older (1). Although benign, the tumor can cause significant morbidity due to its location on the vestibular division of the eighth cranial nerve in the internal auditory canal (4, 7, 8). In the present study we examine unilateral sporadic acoustic neuroma which comprises 90-95 percent of all acoustic neuromas (1, 9).

The only well-established exogenous risk factor for acoustic neuromas is ionizing radiation. A link between acoustic neuroma and mobile phone use has been suggested, although the increased risk, if real, seems to be associated with longer duration of use, generally 10 or more years of use prior to diagnosis (10, 11). In the present study we focus on occupational noise exposure as a potential risk factor for acoustic neuroma. Two previous studies have examined occupational noise and its relationship to acoustic neuroma with consistent results (12, 13). In the first study elevated risks for acoustic
neuroma were found for occupational noise exposure based on self-reported occupational histories reviewed by an occupational hygienist (13). In the second study elevated acoustic neuroma risks were detected for self-reported regular exposure to occupational and nonoccupational noise (12). In both studies a dose-response effect was evident with increasing years of noise exposure (12, 13). Limitations of the prior studies include their use of self-reported exposure, as both studies analyzed participant interview data.

The purpose of the present study was to investigate exposure to objectively measured occupational noise and acoustic neuroma risk in a large register based case-control study. This would facilitate further examination of the role of noise in acoustic neuroma etiology.

3.3 Materials and Methods

3.3.1 Study Design and Population

A register-based, case-control study was conducted in which the source population included all residents of Sweden between 1987 and 1999 who were gainfully employed according to any census performed between 1975 and 1990. The study was approved by the Ethics Committee at the Karolinska Institutet.

3.3.2 Acoustic Neuroma Case Ascertainment

Eligible cases included all patients diagnosed with acoustic neuroma (ICD9 code 1920 and histopathological code 451, classified according to WHO/HS/CANC/24.1 histology code) between 1987 and 1999. We identified 793 cases of acoustic neuroma reported to the national Swedish Cancer Registry who met these criteria. In Sweden physicians and pathologists must
notify the Cancer Registry of every case of acoustic neuroma. In our study, reference year was defined as the year of acoustic neuroma diagnosis.

3.3.3 Controls

Controls were selected randomly from the continuously updated Swedish Population Registry from among individuals never diagnosed with acoustic neuroma or other intracranial tumors, pancreatic cancer, or hematological malignancies (controls were selected simultaneously for studies of the latter two tumor types, as part of another larger case-control study). On December 31 of each year of the study, controls were frequency matched on age and sex to cases of acoustic neuroma, pancreatic cancer, and hematological malignancies diagnosed during that year. The year a control was selected was used as the reference year for the control. Controls could only be selected once and cases could not be selected as controls. Registry information necessary for the analysis was readily available, as all study participants could be linked to other Swedish registers by means of the national registration number unique to each individual in Sweden (14). In our study the entire set of controls ($n=101,756$) was used.

3.3.4 Census Data

The study participants’ occupations were obtained from censuses performed by Statistics Sweden in 1975, 1980, 1985, and 1990. Census data, collected in September of each census year, provided the occupational codes and socioeconomic statuses for the study participants. Occupations were categorized using a three-digit occupational coding system.

3.3.5 Job Exposure Matrix

The job exposure matrix (JEM) used in this study was a cross-classification between numerous occupations and actual noise measurements taken during different time periods. The noise exposure information used for construction of the JEM derives from measurements performed from the late 1960s
and onward all over Sweden at occupational medicine clinics and occupational health services units. The exposure estimate for a 5 year period was based on all available measurements for that period. The estimated decibel (dB) level for each occupation during each of the 5 year time periods was coded as either <75 dB, 75-84 dB, or ≥85 dB based on the consensus of three occupational hygienists. This JEM covers 320 different occupations, with up to four different measurements made per occupation.

3.3.6 Individual Noise Exposure Assessment

Instead of depending on self-reported noise exposure as was done in prior studies, occupational exposure in the present study was based on knowledge of job titles (15, 16). Information regarding noise exposure for each study participant was assessed by linking the newly created JEM to each subject’s occupational code in each of four censuses. Exposure could be determined by the occupation at each census and by the noise measurement for each occupation during the pericensal time period. For each occupation, noise measurements were made for the 5 year periods preceding and following each of the 4 census years. Consequently, individual exposure data were not available for 1995 to 1999 (the last follow-up period), as 1990 was the last census from which occupational codes were available. In addition, only exposure occurring prior to the reference date was considered in the analysis. Unfortunately, data on noise-induced hearing loss among study participants were not available for use as an indicator of noise exposure.

Although occupation was reported only every 5 years, if the noise measurement for an occupation was ≥75 dB for the 5 years before the census, then a study participant reporting that occupation could be considered exposed at each of the 5 years prior to the census. Equivalently, if the noise measurement for the 5 year period was after the census,
the study participant could be assigned the noise measurement for that occupation for the 5 years including and following the census. However, exposure status for an occupation could not be based on an average of both the years preceding the census and following it, as combining exposure statuses for the years preceding and following a census might lead to further exposure misclassification.

All analyses were all performed initially in two ways, first assigning exposure before the census and then assigning exposure for the period including and following the census. Differences in risk estimates and accompanying 95 percent CIs between the two times of exposure assignment were negligible. Therefore, we arbitrarily selected the dB measurement categories for the 5 years preceding each census to assess exposure in the final model.

In the present analysis, ever being exposed to low noise versus never being exposed was defined as ever holding an occupation with exposure between 75 and 84 dB based on any census, compared to never having an occupation with noise exposure. Ever being exposed to high noise versus never being exposed was similarly defined using exposure of $\geq 85$ dB.

To evaluate the impact of different latency periods we examined the effect of time since first noise exposure on acoustic neuroma risk. Given the length of the observation period (1975-1990), the semidecadal censuses, and based on estimates of the latency period for acoustic neuroma reported in prior studies, latency periods of 5, 10, and 15 years were chosen (12, 17, 18). A 20 year latency period was not used, as there were too few observations for meaningful analysis. In the analysis, risk estimates for low noise exposure as well as for high noise exposure were obtained for each of the three latency
periods, as well as for no latency period. The reference category for each comparison in this analysis included those whose first exposure was within the latency period as well as those never exposed. The latency period analysis assumes implicitly that exposure during the latency period has no effect on the developing tumor. Finally, the availability of occupational data from multiple consecutive censuses allowed for the assessment of exposure duration, in which we investigated the effect of low noise exposure and high noise exposure at one, two, three, and four consecutive censuses prior in time to the reference year.

3.3.7 Statistical Analysis

Unconditional logistic regression models adjusted for age, sex, and socioeconomic status were used to estimate odds ratios (OR) and their respective 95 percent confidence intervals (CI) with SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina) (19). The OR was used as an estimate of relative risk in the analysis of the JEM data. Age was evaluated for inclusion in the model as both a categorical and a continuous variable. As there was a negligible difference between these two representations of age and in order to reduce the number of variables, age was included as a continuous variable in the final model. Socioeconomic status was categorized into eight groups as shown in Table 3.1. All statistical significance tests were two-sided.

3.4 Results

Basic demographic characteristics of cases and controls are presented in Table 3.1. The total number of cases and controls in the study was 793 and 101,756, respectively. The ages of the cases ranged from 21-84 years. Differences among the
demographic variable distributions between cases and controls can be seen for age and sex because controls were matched on these variables also to types of tumors other than acoustic neuroma. Of all study participants, less than one percent were missing information on occupation and approximately two percent were missing information on socioeconomic status. The JEM enabled 72 percent of the study participants to be assigned an exposure level, allowing 599 cases and 73,432 controls to be included in the final analysis. There were no meaningful differences in the distributions of sex, age, or socioeconomic status between all study participants and those with information on exposure.

Table 3.2 shows the most frequent occupations with high (≥ 85 dB) noise exposure according to case status and sex. Men were significantly more often employed in occupations with high noise ≥85 dB (14 percent of men and 3 percent of women), as well as in occupations with low (75-84 dB) noise (63 percent of men and 43 percent of women).

In Table 3.3 the OR for ever being exposed to low noise and the OR for ever being exposed to high noise were both slightly below unity and the CIs included the null. Odds ratios are presented for acoustic neuroma according to time since first noise exposure or latency period. All of the CIs for the three latency periods for both low and high noise included the null.

Odds ratios for acoustic neuroma are presented in Table 3.4 for exposure to occupational noise according to one, two, three, or four consecutive censuses closest in time prior to reference year. The ORs for the four low noise exposure durations were slightly above unity but all of the corresponding CIs included the null. For the high noise
exposure category the ORs were generally at or close to unity and again the CIs all included the null. As part of the analysis Tables 3.3 and 3.4 were combined (i.e., duration of exposure stratified on latency period), however the numbers of observations were too small for meaningful analysis.
Table 3.1. Selected characteristics of all study participants and of the study participants with information on exposure, Sweden, 1987-1999.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eligible (n=793)</td>
<td>With exposure information (n=599; 76%)</td>
</tr>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>391 49</td>
<td>332 55</td>
</tr>
<tr>
<td>Female</td>
<td>402 51</td>
<td>267 45</td>
</tr>
<tr>
<td>Number with information on occupation in at least one census</td>
<td>791 99.7</td>
<td>599 100</td>
</tr>
<tr>
<td>Age at reference date (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>20-39</td>
<td>131 17</td>
<td>85 14</td>
</tr>
<tr>
<td>40-59</td>
<td>373 47</td>
<td>306 51</td>
</tr>
<tr>
<td>60-79</td>
<td>282 36</td>
<td>205 34</td>
</tr>
<tr>
<td>≥80</td>
<td>7 1</td>
<td>3 1</td>
</tr>
<tr>
<td>Socio-economic status based on occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unskilled employees in goods and service production</td>
<td>223 28</td>
<td>180 30</td>
</tr>
<tr>
<td>Skilled employees in goods and service production</td>
<td>103 13</td>
<td>96 16</td>
</tr>
<tr>
<td>Assistant non-manual employees</td>
<td>121 15</td>
<td>73 12</td>
</tr>
<tr>
<td>Intermediate non-manual employees</td>
<td>138 17</td>
<td>101 17</td>
</tr>
<tr>
<td>Upper-level executives</td>
<td>77 10</td>
<td>50 8</td>
</tr>
<tr>
<td>Self-employed professionals</td>
<td>38 5</td>
<td>31 5</td>
</tr>
<tr>
<td>Agricultural</td>
<td>23 3</td>
<td>23 4</td>
</tr>
<tr>
<td>Miscellaneous and unclassified</td>
<td>66 8</td>
<td>45 8</td>
</tr>
</tbody>
</table>
### Table 3.2. Most frequent occupations with high (≥ 85 dB) noise exposure among cases and controls for men and women, Sweden, 1987-1999.

<table>
<thead>
<tr>
<th>Cases*</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
</tr>
<tr>
<td>• Construction carpenters and joiners (n=24)</td>
<td>• Construction carpenters and joiners (n=3,778)</td>
</tr>
<tr>
<td>• Bench carpenters and cabinet makers (n=24)</td>
<td>• Forest workers and log-drivers (n=2,554)</td>
</tr>
<tr>
<td>• Forest workers and log-drivers (n=14)</td>
<td>• Bench carpenters and cabinet makers (n=2,308)</td>
</tr>
<tr>
<td>• Sheet metal workers (n=1,744)</td>
<td>• Plumbers and pipe fitters (n=1,503)</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
</tr>
<tr>
<td>• Other production related work (n=4)</td>
<td>• Spellers, weavers, knitters and dyers (n=426)</td>
</tr>
<tr>
<td>• Sheet metal workers (n=3)</td>
<td>• Plastic products workers (n=300)</td>
</tr>
<tr>
<td>• Butchers and meat preparers (n=2)</td>
<td>• Bench carpenters and cabinet makers (n=296)</td>
</tr>
<tr>
<td>• Spinners, weavers, knitters and dyers (n=2)</td>
<td>• Other production related work (n=178)</td>
</tr>
<tr>
<td></td>
<td>• Canning workers (n=168)</td>
</tr>
</tbody>
</table>

* high noise exposure occupations held by more than one case
Table 3.3. Odds ratios and 95% confidence intervals for acoustic neuroma in relation to noise exposure level according to latency period duration, Sweden, 1987-1999.

<table>
<thead>
<tr>
<th>Latency Period</th>
<th>&lt;75 dB</th>
<th>≥75-84 dB</th>
<th>≥85 dB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>Cases</td>
</tr>
<tr>
<td>No latency period</td>
<td>178</td>
<td>16,761</td>
<td>354</td>
</tr>
<tr>
<td>≥5 year latency</td>
<td>180</td>
<td>17,083</td>
<td>352</td>
</tr>
<tr>
<td>≥10 year latency</td>
<td>212</td>
<td>20,789</td>
<td>327</td>
</tr>
<tr>
<td>≥15 year latency</td>
<td>283</td>
<td>26,929</td>
<td>262</td>
</tr>
</tbody>
</table>

* OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex and socioeconomic status
† CI, confidence interval
‡ reference category includes study participants with first exposure during the latency period and those never exposed
Table 3.4. Odds ratios and 95% confidence intervals for exposure to noise at any time (ever) for one, two, three, or four consecutive censuses closest in time prior to reference year, Sweden, 1987-1999.

<table>
<thead>
<tr>
<th>Exposed in:</th>
<th>≥75-84 dB‡</th>
<th></th>
<th></th>
<th>≥85 dB‡</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td>OR*</td>
<td>95% CI†</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>One census</td>
<td>250</td>
<td>23,740</td>
<td>1.13</td>
<td>0.86, 1.49</td>
<td>25</td>
<td>2,578</td>
</tr>
<tr>
<td>Two censuses</td>
<td>183</td>
<td>16,711</td>
<td>1.18</td>
<td>0.88, 1.58</td>
<td>15</td>
<td>1,496</td>
</tr>
<tr>
<td>Three censuses</td>
<td>131</td>
<td>11,955</td>
<td>1.21</td>
<td>0.88, 1.66</td>
<td>10</td>
<td>1,026</td>
</tr>
<tr>
<td>Four censuses</td>
<td>100</td>
<td>10,006</td>
<td>1.15</td>
<td>0.81, 1.63</td>
<td>9</td>
<td>796</td>
</tr>
</tbody>
</table>

* OR, odds ratio, from unconditional logistic regression analysis, adjusted for age, sex and socioeconomic status
† CI, confidence interval
‡ reference category includes 178 cases and 16,761 controls never exposed to occupational noise (i.e., exposure <75 dB)
3.5 Discussion

3.5.1 Occupational Noise Exposure and Risk of Acoustic Neuroma

The present study is the third to examine the association between noise exposure and acoustic neuroma. No evidence was found of an increased acoustic neuroma risk among study participants working in occupations with noise exposure, regardless of exposure level, exposure duration, or latency period. This is in contrast to previous studies examining the role of noise exposure as a possible risk factor for acoustic neuroma that demonstrated an elevated risk of the tumor with exposure to either occupational or nonoccupational noise, or both (12, 13).

In the first study to examine noise in the etiology of acoustic neuromas by Preston-Martin et al. controls were matched to cases aged 25-69 years diagnosed with acoustic neuroma (13). Self-reported occupational histories were reviewed by an occupational hygienist to determine if significant noise exposure occurred. The study found an OR of 2.2 (95 percent CI: 1.12, 4.67) for ever having a job involving exposure to extremely loud noise. The authors also found a dose-response effect for years of employment in an occupation with noise exposure ($P$ for trend = 0.02) (13).

In the second study, occupational and nonoccupational noise exposure were evaluated in a population based case-control study of 146 men and women aged 20-69 years with acoustic neuroma (12). Type and duration of noise exposure were ascertained through self-report with noise defined as $\geq 85$ dB. Exposure to regular noise from machines, power tools and/or construction was found to increase acoustic neuroma risk (OR = 1.79, 95 percent CI: 1.11, 2.89), as did regular exposure to loud music (OR = 2.25, 95 percent CI: 1.20, 4.23). When latency period was examined, an increased acoustic
neuroma risk was found only with a latency of at least 13 years between first regular
noise exposure and the time of diagnosis, with an OR of 2.12 (95 percent CI: 1.40, 3.20)
(12).

The first study by Preston-Martin et al. contained a relatively small number of
cases ($n=86$) and was restricted to men (13). In the second study of both men and women,
data on 146 cases of acoustic neuroma were analyzed, although the number of men in the
study was in fact smaller than the first study (12). It is important to note that while the
total number of cases in the second study ($n=146$) was considerably less than the present
study ($n=599$), the statistical power of the second study was in fact higher due to the
larger number of cases ($n=74$ or 51 percent) exposed to $\geq 85$ dB than in the present study
($n=67$ or 11 percent). The negative findings of the present study may therefore be due to
lack of statistical power.

The strengths of our present study include the high quality of data available for
analysis. Data obtained from the Swedish Cancer Registry have high coverage and
accuracy. In excess of 98 percent of histologically confirmed cancers in Sweden are
reported to the Cancer Registry (14). Of all cancer cases reported to the registry,
including both malignant and benign tumors, close to 80 percent are histologically
confirmed (14). Of the acoustic neuromas reported to the Cancer Registry, 99 percent are
histologically confirmed (Swedish Cancer Registry). Although the quality of the registry
is high it is important to note that acoustic neuroma is a benign tumor and may therefore
be diagnosed many years after the tumor has developed or it may never be diagnosed at
all.
The census registries cover the whole population and therefore the information on occupation collected was remarkably complete. The risk of selection bias was minimized through the random selection of controls from the population and the potential for recall bias was eliminated through the use of objectively collected occupational data obtained from censuses. In addition, the JEM included a large number of different occupations and was based on actual measurements of noise.

3.5.2 Comparison of Results to Prior Study of Self-Reported Noise Exposure and Potential for Recall Bias

The present study was conducted, in part, in an effort to replicate the results of the second study of self-reported noise exposure and acoustic neuroma, through the use of a JEM and census data collected independently of disease (12). Accordingly, the first explanation for the negative findings of the present study was the effect of recall bias in the second study. The tendency for patients with a tumor to focus on the reasons that they may have developed the disease was a potential source of recall bias. At the time of the interview, 91 percent of the cases in the second study reported unilateral hearing loss. This may have made the cases more aware of past noise exposures prior to their diagnosis than the controls, of which only 29 percent reported hearing loss (12).

3.5.3 Diagnostic Delay and the Healthy Worker Survivor Effect

Diagnostic delay is the period between the appearance of the first symptom and the time that first medical attention is sought. As the majority of acoustic neuroma tumors grow slowly it is likely that many of the cases had the tumor for several years before a clinical diagnosis was made (18, 20). According to one study, the delay from the first symptom of acoustic neuroma until diagnosis averaged more than 5 years, with a range of 2 to 30 years (17).
In addition, study participants working in high noise exposure occupations may have developed hearing loss or tinnitus and consequently may have left their occupation or transferred to an occupation with lower noise exposure. This potential source of bias is termed the healthy worker survivor effect (21). Such a situation could potentially explain the observed odds ratios below unity when no, or a very short latency period was used in our analyses (22). Additionally, the slow growth of acoustic neuromas may have resulted in the inclusion in the exposure assessment of a time period during which the tumor was already present, in contradiction to study methodology whereby etiologically relevant exposures are only those prior to disease onset. However, the latency calculation was assigned to address the issue of time between disease onset and diagnosis and furthermore this method of estimating exposure also eliminates bias that results when workers leave their occupations due to noise exposure or symptoms of a tumor (the healthy worker survivor effect).

3.5.4 Misclassification of Exposure and Confounding Another concern is non-differential misclassification of exposure, whereby exposure is misclassified similarly among study participants with and without disease (23, 24). JEMs are often suspected of producing greater non-differential misclassification than do questionnaires (16). When individuals who perform different tasks in different work environments are grouped together under the same occupational title, and are classified as exposed or unexposed depending on whether the probability of exposure exceeds a given threshold (i.e., either 74 or 84 dB), misclassification will inevitably occur (16, 25, 26). If present, misclassification may lead to an underestimation of the effect estimate with associated loss of statistical power (15, 23, 26). Also, in our study nonoccupational noise exposure is
not considered. If there exists a true association between noise and acoustic neuroma, then nonoccupational noise contributes to the risk burden and to exposure misclassification.

Nevertheless, misclassification may in fact be less than anticipated when defining exposure as occupations with noise \( \geq 85 \) dB. Occupations with this noise exposure level are relatively uncommon with only 13 percent of controls classified as such, corresponding to a high specificity. Therefore, even in the unlikely event that a majority of study participants who are classified as exposed are misclassified, most participants classified as unexposed are most likely correctly classified.

It is possible that imprecision of the JEM may be a result of the noise measurements being taken later than the time of the actual exposures, as the noise exposures within each occupation may have changed over time (27). In addition, census data on occupation were obtained every 5 years and reflect the occupational status only at one point in time, and therefore may not accurately reflect the occupational exposure between the censuses or if more than one job was held at the same time (26, 28, 29). There were also a limited number of measurements taken for each occupation. An additional limitation of the study includes the potential for reporting of acoustic neuromas to the Cancer Registry as unspecified tumors. However, such misclassification of cases should be unrelated to exposure.

Finally, as the exposure assessment in the present study was conducted using a JEM, data on the use of hearing protection were not available. In the second study of occupational and nonoccupational noise and acoustic neuroma risk, the OR for study participants exposed to noise with hearing protection was close to the null and therefore
these individuals were categorized as unexposed (12). The observed ORs in the present study that were close to or below the null in the high noise exposure analysis may be attributable, in part, to the use of hearing protection. At an occupational noise exposure level of ≥85 dB and during the years of our study the use of hearing protection would have been commonplace. This, and the aforementioned issues, may contribute to the imprecision inherent in assigning exposure according to occupational categories in a study such as ours, that may ultimately attenuate a true effect.

3.5.5 Conclusion

In summary, the overall results of the study do not support the hypothesis that occupational noise exposure is a risk factor for acoustic neuroma. In the present study we used an objective measure of noise exposure in the form of a JEM. Yet, because we had no direct measure of each individual's exposure to noise, but rather used occupational categories to estimate this exposure, the effect of non-differential misclassification of exposure must be considered as a potential cause of the negative findings.

3.6 Acknowledgments

The study was funded by the Swedish Council for Working Life and Social Research. I thank Helena Pettersson for preparation of the data and Kati Maharry, M.A.S. for assistance with the statistical analysis.
3.7 References


CHAPTER 4

ACOUSTIC NEUROMA: HISTOPATHOLOGY, NATURAL HISTORY, AND THE ROLE OF ACOUSTIC TRAUMA IN TUMORIGENESIS

4.1 Abstract

Loud noise exposure has been shown to increase the risk of acoustic neuromas in two prior studies, however a recent study of occupational loud noise and acoustic neuromas finds no such association. A mechanism of acoustic neuroma tumorigenesis during the cellular repair process following acoustic trauma has been proposed, whereby cellular division results in DNA replication errors which may in turn lead to chromosomal changes essential for neoplastic transformation. Furthermore, it is known that deletions on chromosome 22 are the main causal event in acoustic neuromas. However, the question remains as to whether this proposed mechanism is biologically plausible. The author conducted an extensive search of the published literature with a focus on the epidemiology, histopathology, genetics, nerve origin, natural history, and growth rate of acoustic neuromas, as well as vestibulocochlear nerve pathology and noise-induced cochlear and vestibular damage in acoustic neuroma pathogenesis, in order to evaluate the biological plausibility of the proposed hypothesis that loud noise exposure is a risk factor for acoustic neuromas. The tumor typically involves the vestibular rather than the acoustic division of the eighth cranial nerve, however intralabyrinthine
schwannomas and cochlear nerve schwannomas have been reported in the literature. Oxidative DNA damage in the cochlea and mechanical damage to the organ of Corti have been demonstrated in rodents, as well as lesions in the cochlear epithelium of chickens following intense noise exposure. Additionally, evidence of vestibular damage in rodents has been demonstrated following acoustic trauma. Based on an extensive review of the literature the proposed biological mechanism explaining the association between loud noise exposure and acoustic neuromas is plausible, however further research is needed to first confirm that such an association exists and second to further elucidate the precise biological basis for the association.

4.2 Epidemiology

Acoustic neuroma, also referred to as vestibular schwannoma, has an incidence of 1-20 per million per year (1,2) and occurs most often in patients between the ages of 30 and 68 years (3, 4). The sex ratio (females/males) for acoustic neuromas has been reported to be >1 (4-7). Acoustic neuromas account for 5-10 percent of all intracranial tumors and comprise 71-90 percent of tumors of the cerebellopontine angle (3, 8). The only well-established exogenous risk factor for acoustic neuromas is ionizing radiation. It has been found to increase acoustic neuroma risk among individuals who underwent radiation treatment of tinea capitis during childhood and who developed an excess of benign and malignant brain tumors of various histological types, including acoustic neuromas, and among survivors of the atomic bombings in Japan (9, 10).

A possible association between sex hormones and the growth of acoustic neuromas has been proposed by researchers, based on both epidemiological and clinical
features of the tumor (7). However, evidence demonstrating that hormones influence acoustic neuroma growth is inconclusive (11). One epidemiological line of evidence suggesting that female hormones play a role in the etiology of acoustic neuromas is that the incidence is higher in women than in men (5, 12). The clinical observation that acoustic neuromas seldom become symptomatic before the onset of puberty supports the concept that hormones influence tumor growth (13). In addition, increased growth of acoustic neuromas due to hormonal changes during pregnancy has been described (13, 14). Sporadic reports of estrogen receptors in acoustic neuromas can be found in the literature (15). However, several studies have demonstrated a lack of estrogen and progesterone receptors in acoustic neuromas (7, 14, 16, 17).

Another possible risk factor for acoustic neuroma that has been examined at length in the literature over the past several years is cellular telephone use. A link between acoustic neuroma and the use of cellular telephones has been suggested, although the increased risk, if real, seems to be associated with a longer duration of use, generally 10 or more years of use prior to diagnosis (18, 19). A lesser studied potential risk factor for acoustic neuromas is exposure to loud noise. Two previous studies have examined occupational loud noise and its relationship to acoustic neuromas with comparable results (20, 21).

In the first study, elevated risks for acoustic neuromas were found for occupational loud noise exposure based on self-reported exposures, as well as self-reported occupational histories that were reviewed by an occupational hygienist (21). In the second study elevated risks for acoustic neuromas were found for self-reported regular exposure to both occupational and nonoccupational loud noise (20). The type of
loud noise with the highest risk estimate was regular exposure to loud music with an odds ratio of 2.25 (95 percent confidence interval: 1.20, 4.23) (20). This is particularly significant, as the use of in-the-ear technology listening devices such as MP3 players has increased considerably over the past several years. Therefore, not only is there a risk of noise-induced hearing loss with loud noise exposure, but this research suggests that there exists an increased risk of acoustic neuromas. Furthermore, in both studies a dose-response effect was evident with increasing years of loud noise exposure (20, 21).

4.3 Genetics

The functional loss of a tumor suppressor gene located on the long arm of chromosome 22 is thought to be the cause of all cases of sporadic and NF2-associated acoustic neuromas (11, 19). Mutation in the NF2 gene causes loss of expression of the functional tumor suppressor protein named merlin (for moesin-ezrin-radixin-like protein), also known as schwannomin (30, 31, 39). A member of the protein 4.1 superfamily, merlin presents a high degree of amino-acid sequence homology with the ERM (ezrin, radixin, moesin) proteins that link the cytoskeleton to the cell/plasma membrane (30, 31). Merlin, a protein of 595 amino acids, plays an important role in intracellular signaling, modulation of cell motility, and suppression of mitogenesis in schwannoma cells (30, 37, 39). Therefore, it is thought that a loss of merlin expression in Schwann cells leads to aberrant cell growth and formation of an acoustic neuroma (37).

Chromosome 22 is the second smallest autosome, constituting only two percent of the total human haploid genome (13). However, multiple studies have suggested that the long arm of chromosome 22 contains a relatively high number of functional genes and is
involved in an unexpectedly high number of inherited and acquired cancers in humans (13, 33). In patients with unilateral sporadic acoustic neuromas, the disease is the result of inactivation of both alleles of the NF2 gene by acquired somatic mutations (11, 40). Deletions on chromosome 22 are the main causal event in unilateral acoustic neuromas, but point mutations and occasional missense mutations have also been reported (31, 38). Complete loss of one copy of chromosome 22 is often seen in acoustic neuromas (38, 41). In addition, molecular genetic studies of acoustic neuromas have demonstrated loss of heterozygosity on chromosome 22 (38, 40).

It is important to note that the genomic stability of acoustic neuromas is significant, with chromosomal losses being highly specific for chromosome 22 (33, 42). In a study of 43 acoustic neuroma patient samples the authors found extensive deletions involving most or all of the long arm of chromosome 22 in most tumors with chromosome 22 loss (40). An investigation of the tumor suppressor genes VHL, APC, WT2, and NF1 in these 43 samples suggested that they are not important in the pathogenesis of acoustic neuromas (40). In addition, a number of studies of the p53 tumor suppressor gene have demonstrated that it too does not play a central role in acoustic neuroma tumorigenesis (13, 40). Finally, an analysis of the role of the PTEN tumor suppressor gene in the tumorigenesis of sporadic acoustic neuromas found that PTEN was not altered in the 30 tumors studied (43).

Cytogenetic studies of acoustic neuroma have suggested that chromosomes 11, 13, and 19 could be involved in acoustic neuroma tumorigenesis, in addition to chromosome 22 (38). Also, a study of loss of heterozygosity in 76 acoustic neuroma tumors showed 10 percent of tumors with gain of 9q34, a gain frequently seen in a
variety of solid tumors, including colorectal cancer, prostate cancer, parathyroid adenomas, lung adenocarcinomas, non-Hodgkin’s lymphomas, and adrenal cortical tumors (38). However, other than chromosome 22, no consistent regions of interest have been identified through the analysis of a large number of tumors (38).

The concept of the multistep pathogenesis model whereby tumors result from mutations in several tumor suppressor genes and proto-oncogenes holds true for benign tumors, as well as for malignant tumors (40). Therefore, mutation in the \( NF2 \) gene may be only the initial step in a series of events that result in the development of an acoustic neuroma (13). The identification of the other interacting genes whose expression are deregulated during tumorigenesis will lead to a more comprehensive understanding of why \( NF2 \) mutation leads to the formation of this tumor (31).

4.4 Histopathology

Acoustic neuromas are histologically benign neoplasms of the neurolemmal sheath of the eighth cranial nerve (5, 22, 23). It is important to note that there are two distinct clinical presentations for acoustic neuromas. Approximately 95 percent of diagnosed acoustic neuromas are sporadic, nonfamilial, and unilateral (1, 24). The remaining four to five percent of patients exhibit bilateral acoustic neuromas associated with the inherited syndrome named neurofibromatosis type 2 (NF2) (1, 8).

The distal part of the eighth nerve is comprised, in part, by Schwann cells, that sheath the axons (8, 25). These multivalent neuroectodermal cells are considered homologous to oligodendroglia of the central nervous system, both of which form and maintain the myelin sheath (26, 27). It is this portion of the nerve where an
overproliferation of Schwann cells leads to the formation of an acoustic neuroma (25).
The tumors are rounded and encapsulated, usually appearing as a single mass, with a
capsule dividing the tumor from the nerves (11, 28). Electron microscopic examination of
the neoplastic Schwann cell reveals a large round or elongated nucleus with a distinctive
nucleolus and finely dispersed chromatin (27). In the extracellular space can be found
numerous collagen units with abnormally long spacing, called Luse bodies (27). The
tumors have a remarkably diffuse yellow appearance and compared to other benign
intracranial tumors acoustic neuromas have the least proliferative status (25, 29).
Additionally, decreased basal apoptosis rates of acoustic neuroma schwannoma cells in
vitro and in vivo have been observed compared to normal Schwann cells (30).

The histological appearance of acoustic neuromas is marked by two prominent
types of tissue. Type A Antoni cells which are composed of a closely packed, cellular,
fibrillar structure, with small spindle-shaped densely staining nuclei, and type B Antoni
cells which are comprised of a less cellular, loosely arranged, reticular structure (8, 25,
29). The same tumor may contain both histological types (12). The loosely arranged
Antoni B tissues may contain extratumoral or intratumoral cysts characteristic of cystic
acoustic neuromas (31).

Acoustic neuromas derive their main arterial blood supply from the basilar
arteries, as well as from the vertebral arteries (8). A relationship between sex and tumor
vascularity has been shown, with fewer blood vessels in tumors of males and twice the
frequency of heavy vascularization in tumors of females (15). In addition, it has been
suggested that angiogenic factors may play a role in tumor growth (1, 32). Additional
factors implicated in the pathogenesis of sporadic and NF2-associated acoustic neuromas
are nerve growth factor, glial growth factor, platelet-derived growth factor, basic fibroblast growth factor, transforming growth factor-β, epidermal growth factor, and vascular endothelial growth factor, however their roles in the pathogenic process require further evaluation (25, 31, 33-36). Additionally, neuregulin-1 (NRG-1) and/or neuregulin-2 (NRG-2) proteins have been suggested as possible growth factors involved in the promotion of acoustic neuroma tumorigenesis (34, 37). It has also been demonstrated that the erbB2 and erbB3 membrane tyrosine kinases to which NRG-1 and NRG-2 bind, are expressed by neoplastic Schwann cells in the majority of acoustic neuromas (34, 37).

Inflammation is a frequent feature found in histological sections of acoustic neuromas and inflammatory tumor components can influence tumor size and growth (32). In a clinicopathologic study of growth factors in 69 acoustic neuroma tumor samples, the authors of one study found a statistically significant correlation between symptom duration of longer than one year and degree of inflammation, which is consistent with the concept that inflammation is a degenerative change (32).

4.5 Pathology of the Vestibulocochlear Nerve

The vestibulocochlear or eighth nerve transmits sensory information essential for balance and hearing and measures approximately 17-18 mm in men and 16-17 mm in women (24, 25). The two branches of the nerve are the vestibular and cochlear that course through the cerebellopontine angle as two distinct nerves (25, 44). The fibers of
both nerves originate in separate end organs and have separate central connections, however they do travel as one nerve through the posterior cranial fossa and internal auditory canal (45).

The cochlear nerve transmits sensory input regarding hearing and the fibers of the nerve originate from the hair cells of the organ of Corti located in the cochlea (44). The vestibular nerve transmits sensory input regarding balance and is usually larger than the cochlear nerve (44, 45). The vestibular branch has two divisions in the internal auditory canal, the superior and the inferior (25, 46). Cadaveric investigations have demonstrated that the superior vestibular nerve is typically larger in size than the inferior vestibular nerve (44). Nerve fibers of the superior and inferior divisions form a single trunk and merge with the cochlear nerve in the internal auditory canal (45). Although the cochlear fibers are smaller, greater in number, and darker staining than the vestibular fibers, the cleavage plane between the fibers of the vestibular and cochlear nerve is not always clear (45, 47, 48).

4.6 Nerve Origin of Acoustic Neuromas

The name “acoustic neuroma” is somewhat of a misnomer as it implies involvement of the acoustic nerve, when in fact the tumor typically involves the vestibular rather than the acoustic division of the eighth cranial nerve (1, 46, 49). The embryologically disordered arrangement of sheath cells in the vestibular nerve predisposes it to develop an acoustic neuroma (50, 51). The tumors are also known as vestibular schwannomas, as they represent a neoplasia of the Schwann cells on the
vestibular nerve (8, 25). As a rule, pure vestibular nerve schwannomas do not infiltrate the cochlear nerve (52). Only in von Recklinghausen’s disease is infiltration of the cochlear nerve found (23, 52).

The exact nerve origin of acoustic neuromas has been the subject of a long standing controversy (53). Although it is now widely accepted that acoustic neuromas originate from the vestibular nerve rather than the acoustic nerve, the precise origin of the tumor on the vestibular nerve is the subject of continued debate. It has been reported that the tumors usually arise on the superior division of the nerve, with fewer tumors arising on the inferior division (12, 51, 54). In contrast, other reports suggest that the majority of tumors arise from the inferior vestibular nerve (46, 48, 55, 56). More recent reports, however, suggest that the tumors arise with equal frequency from the superior and inferior divisions of the nerve (44, 57).

Acoustic neuromas may also originate from the facial nerve (26). In addition, several cases of intralabyrinthine acoustic neuromas have been reported in the literature (49). These are tumors of the vestibular or cochlear nerves that involve the cochlea, the semicircular canals, the vestibule, or a combination of these inner ear structures (59). Finally, cochlear nerve schwannomas have been reported extensively in the literature (59). Although clearly less prevalent than vestibular nerve schwannomas, cochlear nerve schwannomas are not exceptional (50, 55, 60, 61).

4.7 Natural History

The number of reports regarding the growth of acoustic neuromas is numerous, yet the natural history of the tumor remains somewhat controversial (2, 62).
Of all the questions regarding the natural history of acoustic neuromas in the literature, the most important involve to the relationship between tumor growth rate, tumor size, and patient age (63). Growth studies cannot replicate the complete natural history of acoustic neuromas, yet they can uncover details about tumor growth, growth rates, and growth patterns during a defined observation period (25). In order to discern the natural history of acoustic neuromas there must first be an understanding of the environment in which the disease develops, including the normal anatomy and histology of the vestibular nerve, as well as the growth factors involved in tumor development (25).

Histopathological studies of temporal bones have shown the prevalence of acoustic neuromas to be from 0.57 to 2.7% (62, 63). When comparing the clinical incidence of acoustic neuromas, to the prevalence of occult acoustic neuromas from histopathological studies of temporal bones, it can be concluded that the vast majority of tumors that exist are never clinically manifested (62, 64). This is due to the very slow or arrested growth of acoustic neuromas, with potentially less than one percent of tumors acquiring enough growth to become clinically active (62, 63). However, the rapid development of more advanced imaging studies has led to the identification of tumors that would have previously remained clinically undetectable (62). In a study of 164 patients the average diameter of the tumors gradually decreased from 33 mm in 1980 to 22 mm in 1992 (65). During the whole study period CT scanning was available, however during the latter years of the study magnetic resonance imaging (MRI) became the gold standard for imaging acoustic neuromas, thus allowing the detection of tumors with a diameter of only a few millimeters (65).
4.8 Growth Rate

The majority of clinical studies of acoustic neuroma growth rate have used serial imaging, either by means of MRI or computed axial tomography (CT) imaging (66-68). Radiologic surveillance is a mode of conservative management involving the serial assessment of tumor growth by radiologic imaging, in conjunction with periodic clinical assessment of symptom progression (69). Serial radiologic imaging follow up intervals for patients who have had surgery, irradiation, or who are undergoing observation may range from every three to six months initially to every one to two years (1, 11, 66). However, the intervals between follow up are highly dependent on the patient’s clinical course (1). It has been suggested that follow up by MRI can be terminated after five years, as tumor growth occurs only within the first four years after diagnosis (2). Other studies suggest that when tumor growth occurs it does so within the first year of follow up (67, 70). Nevertheless, it is important to note that serial imaging follow-up should not be terminated based solely on tumor quiescence, as some acoustic neuroma patients experience a delayed onset of tumor growth (69).

In addition to classification of acoustic neuromas by size and location, classification of the growth rate of a tumor is one of the most useful tools for clinical management (11). However, the growth of acoustic neuromas, typically measured in mm per year, is largely unpredictable (11, 62). Some tumors may remain unchanged in size for many years, some may regress, some may increase in size at a rate of up to 20 mm in diameter per year, and others may display a variable pattern of growth (2, 11, 62). In a large series of patients reviewed by Charabi et al., five tumor growth patterns were
observed: continuous growth, no measurable growth, no measurable growth followed by
continuous growth, negative growth, and various tumor growth patterns (25, 71).

The percentage of tumors that grow varies widely and has been reported to be
from 15 to 90 percent (2, 63, 72). One factor responsible for the wide variation in growth
rates is the length of the observation period in each study (2, 25). Ascertainment of
growth rate may also depend on the criteria used for the determination of growth (in mm)
(2). Comparison of serial imaging studies is often hindered by the limited numbers of
patients included in each study, the inconsistent inclusion of cystic and NF2 tumors, and
the variation of the imaging modalities used (25, 71). It is also important to note that in
acoustic neuroma growth studies the patients who are assigned to observation only are
selected, with patients receiving immediate surgical or radiation treatment excluded from
such observation groups (73). Yet another problem limiting the evaluation of growth
studies in patients undergoing observation is the absence of a well-defined “endpoint” for
the observation period (25, 71). Many factors can initiate the transition from a period of
observation to surgical intervention, including tumor growth change, histopathologic
change, clinical symptom change, or a change in patient consent for treatment (71).

Monitoring of tumor growth is best achieved with gadolinium-enhanced MRI
(11). Mean annual tumor growth rate can vary from 0.7 mm to 4.8 mm per year (22, 62,
66). Although widely variable, the criterion for determination of tumor growth is often
reported as a change of the largest tumor diameter of more than two mm (2, 66, 69). The
largest anteroposterior and mediolateral dimensions are often used (68, 69, 74). In order
to assess tumor growth most accurately, it has been suggested that the size of the tumor
within the posterior fossa and the degree of penetration into the intracanalicular space
should be evaluated (11, 69). Some groups promote tumor volume (in cubic cm) as the ideal tumor measurement, whereas others find no difference in tumor growth analysis when using either tumor volume or tumor diameter (24, 62, 75, 76). One further method of growth rate analysis is tumor volume doubling time (VDT) which represents the amount of time (in years) it would take for a tumor volume to double if growth were linear (6, 24). Rapidly growing tumors have a VDT of less than 12 months, moderately growing tumors have a VDT of 12-36 months, and slow-growing tumors have a VDT of more than 36 months (6). This is in contrast to volume growth rate for malignant brain tumors which have a VDT of as short as 20 days (75).

Numerous studies examining various aspects of the growth rate of acoustic neuromas can be found in the literature. Several studies report no relationship between tumor size and duration of symptoms (16, 62, 64, 74). Other studies report no correlation between tumor growth and patient age or follow up length (13, 67, 77). Other studies have reported no significant correlation between patient age and tumor size (24, 74). In another study no significant differences in tumor size between males and females were found (44). As a result, it is not possible to demonstrate any pathoanatomic feature of acoustic neuroma that correlates with the clinical course of the tumor (24, 71, 78).

In contrast, other studies have found various correlations between tumor growth rate, tumor size, patient age, duration of symptoms, and patient sex. For example, one study did find a statistically significant inverse relationship between tumor size and patient age (17). Other studies have reported a tendency for higher growth rates in larger tumors and in younger patients (6, 25, 72, 76). Yet another study demonstrated that patients with shorter duration of symptoms had tumors that statistically grew faster (16,
In a study examining possible gender differences in the growth rates of acoustic neuromas a tendency for tumors to grow more rapidly in females than males was observed (6). Another study of 433 patients with unilateral acoustic neuromas found that tumor size was larger in the female than in the male group (17). However, even with such findings no single predictive factor for tumor growth has yet been identified for widespread clinical use (6, 22, 68, 78).

As a result, when attempting to predict the growth rate and choosing a therapeutic option for an acoustic neuroma several factors should be taken into account, including patient age and sex, tumor pathology, hearing level, and tumor size at diagnosis (6, 71). Insight into the growth rate of a tumor must be ascertained, in part, by serial imaging studies and the choice of imaging interval cannot be guided by baseline data (24). Finally, it is important to note that duration of symptoms is uncertain subjective data provided by the patient and the reproducibility of such data is questionable (25, 32).

Diagnostic delay is the period between the appearance of the first symptom and the time that first medical attention is sought. Thomsen and Tos have suggested that a period of one year from the appearance of the first symptom until diagnosis is a situation in which there is no diagnostic delay (64, 78). Any longer period than this and diagnostic delay is considered present. The typical early symptom of an acoustic neuroma is gradual hearing loss which may not interfere enough with the patient’s daily living to justify medical attention (62). As a result, the failure to seek medical attention when such symptoms first appear, combined with the failure of primary care physicians or neurotologists to correctly diagnose the cause of the symptoms, often leads to lengthy diagnostic delays. The average time from onset of symptoms to clinical diagnosis ranges
from approximately 4 to 7.3 years (5, 44, 78). In one study of 233 patients the average diagnostic delay was 7.1 years, with a range of 2 to 30 years (64).

Earlier studies of Schwann cell-related markers were limited to the immunohistochemical recognition of S-100 protein (25). Schwannoma cells characteristically express S-100 protein strongly throughout the tumor (14, 29). More recently, immunohistochemical investigation using the monoclonal antibody Ki-67 has been used to study the growth rate of acoustic neuromas (67, 79). During cell proliferation the nuclear antibody Ki-67 is found on all human cells, whereas it is absent in cells in the G0 or noncycling phase (62). In one study using the Ki-67 technique two growth rates were demonstrated in acoustic neuromas (25). In addition, the cellular proliferative fraction in acoustic neuromas was found to be the least among a group of benign and malignant brain tumors (25). Another study demonstrated a significant relationship between Ki-67 counts and duration of symptoms (25, 62). Tumors with a high proliferative status had a short duration of symptoms, whereas tumors with low proliferative status had a long duration of symptoms (25). In yet another study the macroscopic growth of acoustic neuromas in athymic nude mice was correlated with a high rate of cellular proliferation as expressed by Ki-67 (25).

The proliferating cell nuclear antigen (PCNA) is an auxiliary protein for DNA polymerase. (25). It accumulates in the nuclei of dividing cells predominantly in the S phase of the cell cycle (25). Therefore, PCNA has been used as an indicator of proliferative activity and growth rate of a variety of cancers, including acoustic neuromas (25, 33). The application of PCNA to determine growth rate in two studies revealed proliferation of between 0.00 and 8.87 percent and a statistically significant difference
between the proliferation in tumors smaller than 3 cm and those larger than 3 cm in one study, and an increased rate of PCNA-positive cells in hyperdiploid tumors compared to diploid tumors in a second study (25). Another study of 22 cases of acoustic neuroma demonstrated a relationship between tumor size and the PCNA labeling index (33). The PCNA index provides an estimate of the percentage of tumor cells studied that are in the cell cycle (33). Studies have also demonstrated that tumor growth is not uniformly distributed within a tumor and that proliferation appears to be more active near the surface or in the capsule compared to the center of the tumor (25, 79).

DNA flow cytometric studies have been utilized as an estimate of the proliferative activity of acoustic neuromas as determined by the fraction of tumor cells in the DNA synthetic or S phase of the cell cycle (7, 38). In three studies no correlation was found between the percentage of cells in the S phase of the cell cycle and tumor size, patient age, or duration of symptoms (25). Studies have demonstrated a wide range of S phase fractions suggesting a large variation in the growth potential of the acoustic neuromas examined (80). Finally, studies have suggested that the G1 regulators of the cell cycle, cyclin D1 and cyclin D3, play a significant role in the regulation of Schwann cell proliferation and differentiation (81). The cyclin D1 gene is known to be rearranged, over-expressed, and/or amplified in a number of human malignancies and cyclin D3 is known to be over-expressed and/or amplified in some tumors (81).

4.9 Noise-induced mechanical damage of the cochlea

Oxidative DNA damage has been demonstrated in the cochlea of rodents following intense noise exposure (82, 83). Yamashita et al. (2004) demonstrated that
mechanical trauma occurring during loud noise exposure is accompanied by oxidative stress-induced formation of reactive oxygen species (ROS). These reactive species directly cause cell damage by destroying DNA, as well as cell membranes. They also act as signaling molecules for the upregulation of genes involved in apoptosis. Cochlear damage following intense noise exposure continues to spread for a period of days along the cochlear turn, even after the noise exposure is terminated. Free radical reactions are fast and transitory, typically terminating within milliseconds to seconds. Therefore, either newly formed ROS continue to appear even after the noise exposure has ceased, or other delayed biochemical events occur that cause cell damage (83). In addition, it has been suggested by Fujioka et al. that noise-induced cochlear damage may involve an early-phase inflammatory response. A key regulator in inflammation is the fibroblast that produces several cytokines. Proinflammatory cytokines are released in a number of organs following tissue damage. Several reports suggest that proinflammatory cytokines such as IL-6, IL-1β, and TNF-α may initiate an inflammatory response after loud noise exposure and thus may be involved in cochlear damage (84).

4.10 Acoustic Trauma in the Pathogenesis of Acoustic Neuroma

A study of intense noise exposure in chickens found that lesions were produced in the cochlear epithelium (85). Furthermore, it has been reported previously that damage to cochlear hair cells produced by acoustic trauma stimulates mitotic replication of normally postmitotic cells in the chicken and quail (85, 86). The supporting cells or perhaps unidentified stem cells that have been found to replicate as a result of the acoustic trauma, do not divide in the absence of trauma (85). As a result of this discovery in the avian
cochlea the possibility of self-repair of hair cells following acoustic trauma in mammalian ears should not be ruled out (85).

Experimental studies in rodents have demonstrated mechanical damage to the organ of Corti and surrounding tissue as a result of intense impulse noise (87-89). Damage to the structures of the ear caused by intense sound exposure appears to be caused by similar mechanisms in all mammals (90). In addition, myelin-related Schwann cell proliferation during Wallerian degeneration has been shown in tissue culture in response to direct injury to the cells (91). In these tissue models, damaged Schwann cells were replaced and new basal lamina and myelin were produced (91).

The majority of published studies have focused on cochlear damage following loud noise exposure, with few studies addressing vestibular damage (92). In a study by Watanabe et al. (2004), an immunohistochemical examination of the vestibules of guinea pigs was performed after acoustic stimulation. In the study inducible nitric oxide synthase (iNOS) was detected in the vestibules of the noise exposed group, but not in the vestibules of the control group. iNOS generates large amounts of nitric oxide, a free radical that reacts with superoxides, resulting in damage to surrounding tissues. Pathological processes such as inflammation are thought to promote the expression of iNOS. The findings of this research indicate that the expression of iNOS participates in the pathogenesis of vestibular damage resulting from acoustic trauma (92). Additional evidence of vestibular damage following acoustic trauma was found in an electronystagmographic study of 326 men suffering from acoustic trauma, in which evidence of vestibular injury was found in combination with cochlear damage (93). Also, inflammation has been shown to be a recurrent hallmark of acoustic neuromas on
histological sections, especially in Antoni type B areas, and inflammatory components have been shown to influence benign tumor growth (32).

If cancer risk is proportional to the number of proliferating cells, as has been previously postulated (94), then it is plausible that a benign tumor such as AN may arise as a result of cochlear or vestibular acoustic trauma. During the cellular repair process, cellular division results in DNA replication errors which may in turn lead to chromosomal changes essential for neoplastic transformation (20, 21). This hypothesis is consistent with the common mechanism of tumorigenesis that exists for all acoustic neuromas. Selective losses of genes on chromosome 22 result in loss of expression of the NF2 gene product and functional tumor suppressor protein merlin, in combination with the deregulation of other interacting genes, ultimately resulting in tumor formation (42, 43). In the case of sporadic unilateral acoustic neuromas, loss of genes on chromosome 22 can be viewed as analogous to that of genes on chromosome 11 in Wilms’ tumor and chromosome 13 in retinoblastoma (42).

4.11 Conclusion

In conclusion, although the majority of acoustic neuromas are found on the vestibular nerve, intralabyrinthine schwannomas (including cochlear schwannomas), and cochlear nerve schwannomas have been reported. Two published manuscripts have suggested a hypothesis for a mechanism of acoustic neuroma tumorigenesis following cochlear or vestibular acoustic trauma (20, 21). The same hypothesis can be applied to acoustic neuromas located on the vestibular nerve, as studies have demonstrated vestibular damage, in addition to cochlear damage, following acoustic trauma (92, 93).
To summarize, in NF2-associated acoustic neuromas a patient inherits a chromosome 22 that has a deleted or mutated NF2 locus and then a random mutation of the remaining NF2 locus removes the inhibition provided by the NF2 gene product merlin (42, 43). In patients with unilateral sporadic acoustic neuromas, the disease is the result of inactivation of both alleles of the NF2 gene by acquired somatic mutations (11, 40). Thus, the mechanism of tumorigenesis acts in accordance with Knudson’s “two hit” mutation model, identical to the retinoblastoma model of carcinogenesis involving chromosome 13 (15, 21).

Also, with only a small fraction of all acoustic neuromas demonstrating enough growth to become clinically active, the identification of such tumors is important. Features that can potentially distinguish tumors with fast tumor growth from those with slow or arrested growth include the influence of growth factors, tumor vascularity, inflammation, basal apoptosis rates, hormones, cystic components, cyclins, and membrane tyrosine kinases (3, 25, 30-37, 58, 81). When examining risk factors that may increase the likelihood of tumor diagnosis, the only endogenous or exogenous factors associated with the features of fast-growing tumors are patient sex and repeated environmental damage to the vestibulocochlear nerve that may lead to chronic inflammation, as has been shown with loud noise exposure. Finally, further studies are needed to confirm that there exists an association between loud noise exposure and acoustic neuroma, as well as to elucidate the precise biological basis for the proposed mechanism of tumorigenesis.
4.12 References


5.1 Summary of Key Study Findings

A study of loud noise and acoustic neuromas performed in 1989 using self-reported loud noise exposures and occupational histories reviewed by an occupational hygienist found an increased risk of acoustic neuromas (1). In an effort to further evaluate the association between loud noise exposure and acoustic neuromas, a larger study was performed using self-reported exposure to occupational and nonoccupational loud noise (2). The second study, the largest study of loud noise and acoustic neuroma risk to date, also found an increased risk of acoustic neuromas (2). Furthermore, in both studies a dose-response effect was evident with increasing years of loud noise exposure (1, 2).

In order to validate the self-reports of loud noise exposure used in the second study, a more objective study of occupational noise exposure and risk of acoustic neuromas was conducted using a job exposure matrix. The third study, however, did not demonstrate an increased acoustic neuroma risk related to occupational noise exposure, even allowing for a long latency period. In summary, two studies using self-reported loud noise exposure have demonstrated an association between loud noise exposure and acoustic neuromas, however, one study using a more objective measure of noise exposure found no such association (1, 2). As a result of these findings, it was suggested that
additional studies are needed to confirm that there exists an association between loud noise exposure and acoustic neuromas. Additionally, a recommendation that further research is needed to evaluate the effect of potential detection bias was made.

5.2 Summary of the Role of Acoustic Trauma in Acoustic Neuroma Tumorigenesis

As a result of the inconsistent study conclusions, an investigation into the biology of acoustic neuromas was conducted. The histopathology, natural history, and role of acoustic trauma in acoustic neuroma tumorigenesis were reviewed in the medical literature. The hypothesis proposed in the first study and in the study described in Chapter 2 suggested that following cochlear or vestibular acoustic trauma and during the cellular repair process, cellular division results in DNA replication errors which may in turn lead to chromosomal changes essential for neoplastic transformation (1, 2). This hypothesis is consistent with the common mechanism of tumorigenesis that exists for all acoustic neuromas whereby selective losses of genes on chromosome 22 result in loss of expression of the NF2 gene product and functional tumor suppressor protein merlin, ultimately resulting in tumor formation (3, 4).

However, this proposed mechanism of tumorigenesis has been challenged, as the primary location of acoustic neuromas is on the vestibular division of the eighth cranial nerve, not on the acoustic division (5, 6). In a published criticism of the study described in Chapter 2, the author states that “There is no obvious relation between the stimulus of sound and the development of a tumor in fairly distant cells surrounding a nerve that has nothing to do with hearing.” (6). Although it has been shown in the literature that the majority of acoustic neuromas are found on the vestibular nerve, intralabyrinthine
Schwannomas, including cochlear schwannomas, and cochlear nerve schwannomas have been reported (7, 8). It is therefore plausible that acoustic trauma to the labyrinth or acoustic nerve could contribute to the development of an intralabyrinthine or cochlear nerve schwannoma. Additionally, in support of the plausibility of this hypothesis, it is important to note that with the majority of acoustic neuromas located on the vestibular nerve, studies have nevertheless demonstrated vestibular damage in addition to cochlear damage, following acoustic trauma (9). Thus, in addition to confirming the association between loud noise exposure and risk of acoustic neuromas, additional studies are needed to elucidate the precise biological basis for the proposed mechanism of tumorigenesis.

5.3 Study Limitations and Recommendations for Future Research

The analysis of the first acoustic neuroma data set presented in Chapter 2 reinforced the significance of one of Hill’s criteria for causation, namely biological plausibility. When conducting epidemiologic research it is important that careful consideration be given to the biological basis for any proposed causal hypothesis. A statistically verified association, as was found in the study, must be accompanied by a sound, biologically plausible hypothesis for the mechanism of tumorigenesis.

In addition, caution must be taken when reporting the findings of epidemiologic research, as published research is often disseminated rapidly by the media and can have widespread public health and legal implications. Although consistency of association increases the likelihood that an association is causal, a demonstrated association merely supports a proposed hypothesis, it does not prove it. The findings of the study reported in Chapter 2 were consistent with the findings of the first study evaluating the association.
between loud noise exposure and acoustic neuromas. This did not, however, prove that loud noise causes acoustic neuromas, only that further research examining the association was perhaps warranted.

In the analysis and discussion of the two studies presented, it was necessary to carefully address the potential weaknesses of the exposure assessment methodologies used, as well as the effect of potential biases, including confounding. Examples of potential epidemiologic problems encountered in this research include recall bias, detection bias, selection bias, non-differential exposure misclassification, and confounding from the healthy worker survivor effect. Epidemiologic problems such as non-differential exposure misclassification can cause an underestimation of the effect estimates, or even a reverse association, as can result from the healthy worker survivor effect for example (10).

Finally, in the study of occupational and nonoccupational loud noise exposure and acoustic neuroma risk presented in Chapter 2, the highest risk estimates were found for regular exposure to loud music, including employment in the music industry (2). Research is needed on the health effects of exposure to in-the-ear technology devices, such as MP3 players. Not only is there a risk of noise-induced hearing loss with loud noise exposure, but this research suggests that there exists an increased risk of acoustic neuromas. However, with the introduction of MP3 players in the late 1990s, it will be undoubtedly be many years before a clear picture of the health effects of these popular devices will emerge.
5.4 References


LIST OF REFERENCES


Tallan EM, Harner SG, Beatty CW. Does the distribution of Schwann cells correlate with the observed occurrence of acoustic neuromas? Am J Otol 1993;14:131-134.


