**Research:**
Hardell Study on Risk Factors for Brain Tumors

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Posted:
29 August 2000

The Hardell Study

There are few studies (yet) which examine the risks of cell phone exposure and the incidence of brain tumors. Dr. Lennart Hardell, of the Orebro Medical Center in Sweden, is one of the few who has pursued research in this area. He found that use of a cellular phone "was associated with an increased risk." His study (from the pages of the Medscape website) is presented below.

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**Original Article**

**Case-Control Study on Radiology Work, Medical X-ray Investigations, and Use of Cellular Telephones as Risk Factors for Brain Tumors**

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[MedGenMed, May 4, 2000. © Medscape, Inc.]

## Abstract

**Context**. Ionizing radiation is a well-established risk factor for brain tumors. During recent years, microwave exposure from the use of cellular telephones has been discussed as a potential risk factor.

**Objective.** To determine risk factors for brain tumors.

**Design.** A case-control study, with exposure assessed by questionnaires.

**Participants.** A total of 233 currently living men and women, aged 20 to 80 years, were included. The case patients had histopathologically

verified brain tumors and lived in the Uppsala-Orebro region (1994-1996) or the Stockholm region (1995-1996). Two matched controls to each case were selected from the Swedish Population Register.

**Main Outcome Measures.** Ionizing radiation and use of cellular telephones as risk factors for brain tumors.

**Results.** A total of 209 cases (90%) and 425 controls (91%) answered the questionnaire. Work as a physician yielded an odds ratio (OR) of 6.00, with a 95% confidence interval (CI) of 0.62 to 57.7. All three case patients had worked with fluoroscopy. Radiotherapy of the head and neck region yielded an OR of 3.61 (95% CI, 0.65-19.9). Medical diagnostic x-ray examination of the same area yielded an OR of 2.10 (95% CI, 1.25-3.53), with a tumor induction period of 5 years or more. Chemical industry work yielded an OR of 4.10 (95% CI, 1.25-13.4), and laboratory work yielded an OR of 3.21 (95% CI, 1.16-8.85). Ipsilateral use of cellular telephones increased the risk for tumors in the temporal, temporoparietal, and occipital lobes (OR, 2.42; 95% CI, 0.97-6.05), ie, the anatomic areas with highest exposure to microwaves from a mobile telephone. The result was further strengthened (OR, 2.62; 95% CI, 1.02-6.71) in a multivariate analysis that included laboratory work and medical diagnostic x-ray investigations of the head and neck.

**Conclusion.** Exposure to ionizing radiation, work in laboratories, and work in the chemical industry increased the risk of brain tumors. Use of a cellular telephone was associated with an increased risk in the anatomic area with highest exposure.

**Keywords:** Brain tumors, fluoroscopy, radiologist, radiation, medical x-ray, cellular telephones

## Introduction

Ionizing radiation is the only established risk factor for brain tumors. The highest risk has been reported for meningioma.[1,2] Recently, 2 cases of brain tumor diagnosed in 1997 among Toronto, Ontario, cardiologists were reported.[3] This might be a chance finding, but since both were occupationally exposed to radiation, a causal association with such exposure could not be excluded.

Some reports have associated pesticides and exposure to certain other chemicals with an increased risk for brain tumors.[1] Based on animal studies, the artificial sweetener aspartame has been discussed as a potential risk factor for especially malignant brain tumors.[4] It was introduced in Sweden in 1981 and is now widely used in different types of food, especially in low-calorie drinks.[5]

Recently, we published results from our case-control study on brain tumors and the use of cellular telephones.[6] For ipsilateral use of a cellular phone, an increased risk was found in the anatomic areas with highest exposure, ie, temporal, temporoparietal, and occipital lobes.

In the same questionnaire, lifetime occupational history and exposure to various agents while working and during leisure time were assessed. These results have not been published so far. Moreover, we have now grouped both sides of anatomic area of the brain and analyzed exposure to mobile phones in relation to the ear used for the calls. The matched control was assigned the same anatomic localization as the corresponding case. Finally, multivariate analysis was performed on risk factors for brain tumor in this study. Thus, in the following, we present further results from the investigation.

## Materials and Methods

This study is our first investigation on this topic and will be followed by a much larger study, which is currently in progress. The aim is to test both the feasibility of studying this patient group and some specific etiologic hypotheses, including the use of cellular telephones. When the study started in the Uppsala-Orebro medical region of Sweden, only patients with a malignant brain tumor diagnosed in 1994-1996 were included. Furthermore, they had to have had a histopathologic diagnosis available according to the Cancer Registry at the time of operation and been alive at the study start. The physicians were contacted for permission to include the patient in the study. Two controls to each case were drawn from the population register. They were matched for sex and age and lived in the same geographic area of Sweden as the cases.

To include a larger study area, the Stockholm medical region was included for the study period (1995-1996). Only patients with a malignant brain tumor were included initially. The same procedure for assessment of exposure was used as in the Uppsala-Orebro region.

The World Health Organization (WHO) contacted us in 1997 regarding a study of exposure to cellular telephones and the risk of brain tumors, which we agreed to participate in. WHO decided to start with a feasibility study, and our ongoing study on brain tumors was included as part of that study.[7] However, benign brain tumors were also included in the WHO feasibility study. Thus, in our study we included patients with benign brain tumors who were living in the Stockholm medical area, since assessment of data was still ongoing in that part of the investigation. Therefore, assessment of exposure was obtained for patie nts with both malignant and benign brain tumors during the same period. However, we included only patients with benign brain tumors diagnosed in 1996 to fulfill the time criteria for the feasibility study.[6,7] The study method was the same in the whole inve stigation.

## Assessment of Exposure

The ethical committees approved the investigation. Information on exposures was assessed by a questionnaire sent to both cases and controls. If the answers were unclear, a nurse trained for this purpose supplemented the answers over the telephone. A written protocol was used during the telephone interviews. The questionnaires were blinded to case or control status. After that, we scrutinized all answers to be sure to obtain uniform assessment of exposure for all cases and controls. If the quality of the answers was judged to fulfill our criteria for assessment of exposure, the information was coded and registered for statistical analysis. Otherwise, the questionnaire was returned to the nurse for additional telephone interview.

Regarding medical x-ray examinations, we asked for the anatomic area that had been investigated, the years of the investigations, and the total number of x-ray examinations. Subjects who had worked as physicians were asked about radiology work.

For cellular phones, use while working and during leisure time, years of use, and mean number of minutes of daily use were assessed. Cumulative use in hours was calculated. Furthermore, we asked for information regarding use of a hands-free device with an earpiece and use in a car with fixed antenna, both taken as unexposed. In one question, we asked which ear was most frequently used during cellular telephone calls. Also, type of telephone, NMT (analogue) or GSM

(digital) system, was assessed.

Exposure to different agents, eg, brand or chemical names, working conditions, and years and number of days per year of exposure were assessed. Since most low-calorie drinks contain aspartame,[5] information on drinking habits was obtained. Years of intake, times per day or week, and amount of drink each time were assessed for calculation of total dose.

Interviews and coding of the answers were made without knowing whether the person was a case or a control. All exposures within 1 year before diagnosis were disregarded. The same year was used for both cases and matched controls. Also, total exposure of less than 1 day was dismissed.

After informed consent, copies of x-ray films for tumor diagnosis and his topathologic reports were requested for the cases. Based on these copies, we judged whether the tumor was a new diagnosis or a recurrent disease, determined the anatomic localization of the tumor, and assessed histopathologic diagnosis.

**Statistical Methods**

Conditional logistic regression analysis for matched studies was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) (SAS Institute Inc, Cary, North Carolina). Results for occupations (ever employed for more than 1 year) with at least 10 exposed subjects (cases and controls) and for occupations of a priori interest, such as linemen, are presented. In a multivariate analysis, use of cellular telephones and some exposures with significantly increased risks were analyzed.

**Results**

In total, 270 cases that fulfilled these inclusion criteria were included 2E Of these, 37 patients were judged by their physicians not to be able to participate. Thus, 233 cases and 466 controls remained in the study. The questionnaire was answered by 217 cases and 439 controls. When scrutinizing medical reports, we discovered that 8 cases had recurrent brain tumors. These cases were excluded from further analysis together with their 14 responding matched controls. Thus, the analysis encompassed 209 cases (90%) and 425 controls (91%). The mean age of both cases and controls was 50 years (range, 21-80 years).

As displayed previously.[6] histopathologic reports were obtained for 197 patients, 136 with malignant and 62 with benign tumors (1 case had 2 benign tumors: ependymoma and acoustic neurinoma). Anatomic tumor localization was assessed for 198 patients: 99 with tumor in the right side of the brain, 78 in the left side of the brain, and 21 with no applicable side (eg, central tumor). The analysis of mobile telephone use and the risk for brain tumor according to anatomic localization was based on these 198 cases with corresponding controls. The whole material of 209 cases and 425 controls was used in the other calculations. The results are presented for all cases with either benign or malignant tumors.

**Occupation**

Occupation as a risk factor was analyzed (Table 1). For physicians, an

OR of 6.00 (95% CI, 0.62-57.7) was obtained. All 3 case patients had worked with x-ray investigations for some period, with tumor induction (latency) periods of 20, 28, and 31 years (Table 2). On the contrary, the only control subject who was a physician had never worked with x-ray investigations.

Overall, work at a radiology department yielded an OR of 1.89 (95% CI, 0. 61-5.89). Excluding the 3 physicians, the 4 cases and 6 controls with other job titles in radiology yielded an OR of 1.24 (95% CI, 0.35-4.43). No increased risk was found for other occupational categories in health services. These job titles were included among nurses or nurse assistants in Table 1.

Electronics, telecommunication, or electrical work did not increase the risk for brain tumors. No subject had worked as a railway engine driver.

For laboratory work, an OR of 3.21 (95% CI, 1.16-8.85) was obtained. Also, work in the chemical industry yielded an increased risk (OR, 4.10; 95% CI, 1.25-13.4).

**Radiotherapy**

Eight cases and 11 controls reported previous radiotherapy for benign or malignant disease, yielding an OR of 1.58 (95% CI, 0.60-4.16). If only the head and neck region was considered, an OR of 3.61 (95% CI, 0.65-19.9) was obtained (4 cases, 2 controls).

**Medical Diagnostic X-ray Investigations**

Overall, no increased risk for brain tumors was found for medical diagnostic x-ray investigations. However, if previous x-ray investigations of the head and neck region were considered, an OR of 1.64 (95% CI, 1.04-2.58) was obtained. Using a tumor induction period of 5 years or more, the risk increased further to an OR of 2.10 (95% CI, 1.25-3.53) based on 36 exposed cases and 37 exposed controls. For the 13 cases with meningioma, an OR of 5.03 (95% CI, 1.60-15.8) was obtained with the 5-year or more induction period.

**Agents**

In Table 3, exposure to different agents is presented. No association was found for exposure to asbestos, pesticides, organic solvents, smoking, or a video display unit. For low-calorie drinks taken as aspartame exposure, an OR of 1.24 (95% CI, 0.72-2.14) was found. The risk was further increased for malignant tumors, with an OR of 2.66 (95% CI, 1.01-7.04) in the highest-exposure group.

**Cellular Telephones**

Table 4 gives the results for use of cellular phones. Increased risk was only found for cases with tumors in the temporal, temporoparietal, or occipital lobe and ipsilateral use of a mobile phone (OR, 2.42; 95% CI, 0.97-6.05). This result was based on 13 exposed cases, 10 with malignant and 3 with benign tumors.[6] Nine cases were exposed to NMT only, 3 to both NMT and GSM and 1 to GSM only. For cont ralateral use, no increased risk was found. Only a few subjects reported both

ipsilateral and contralateral use of a cellular telephone.

**Multivariate Analysis**

Exposure to cellular phones for subjects with brain tumors in the temporal, occipital, or temporoparietal anatomic areas and other exposures with significantly increased risk were included in a multivariate analysis. Work in the chemical industry was not included, since only 1 case with tumor in these lobes and no controls were exposed. Significantly increased risk was found for subjects with ipsilateral exposure to microwaves from a mobile phone (OR, 2.62; 95% CI, 1.02-6.71; Table 5). For laboratory work and medical diagnostic x-ray investigations of the head or neck, a nonsignificantly increased risk was calculated in the multivariate analysis. Similar results were found in the multivariate analysis as in univariate analyses for use of cellular telephone and the risk for brain tumor in other anatomic areas of the brain.

**Discussion**

The purpose of this investigation was not disclosed to the study subjects A questionnaire, which assessed different occupational and leisure time exposures, was used to minimize recall bias. All telephone interviews and coding of the data were made blinded to case or control status to reduce observational bias. Only living patients who were judged to be able to respond to the questionnaire were included to obtain as high-quality data as possible. During the study period, use of mobile telephones was not often discussed in the media as a risk factor for brain tumors.

Thirty-seven patients were excluded because their physicians deemed them ineligible. This might have introduced observational bias in the study if a risk factor is related to the prognosis of the disease for those too ill to participate. However, there are no data in the literature indicating that this is the situation.

Information on radiology work was obtained by the lifetime occupational history. The physicians were interviewed about type of work. Two of 3 cases had worked for only a short period at a radiology department. However, both reported work with fluoroscopy, and the dosimeter of the female case patient showed "always maximal exposure." The third case had worked as an anesthesiologist at radiology departments for about 30% of his working time. Thereby, he had participated during angiographies and heart catheterizations of patients. For other occupational categories at radiology departments, no increased risk was found.

In addition, radiotherapy of the head and neck region was associated with an increased risk for brain tumors, which is in accordance with previous studies.[8-10] Meningioma has been reported to be the most common tumor associated with radiation,[1,2] and 3 of the 4 cases that had been treated with radiotherapy had meningioma in our study.

Medical x-ray investigation of the head and neck region increased the risk, which is in accordance with other results, although the association is somewhat more controversial than for high-dose radiation.[1] Of the patients who reported medical diagnostic x-ray investigations of the head and neck, 36% had meningioma compared with 23% of all cases in this study. The questionnaire data did not allow us to study any dose-response effect, and the reported investigations were not qualified by use of information in patient records. We tried to get information on dental x-ray examinations, but almost all subjects were

exposed, and the number of x-ray examinations was difficult to assess, thus making statistical analysis not meaningful.

In a register study linking census data on occupation with the Swedish Cancer Registry, we did not find an increased risk for brain tumors among physicians.[11] However, we had no data on different specialists, so radiology work could not be studied separately. Ionizing radiation is an established risk factor for brain tumors, asreviewed by Finkelstein[3] and others. [1] Clearly, the report by Finkelstein, [3] other studies, [1] and our results indicate that radiology work, especially fluoroscopy, may be a health hazard and increase the risk for brain tumors. The brain is a part of the body that usually is not shielded during fluoroscopy. Current findings indicate that radiation protection of the head is warranted as precautionary avoidance of exposure but also that further studies to confirm the findings are necessary. Furthermore, studies of dose-response effects should be performed in larger investigations. Also, theoretical calculations of the risk based on dosimeter data on exposure to the brain during fluoroscopy are warranted.

Exposure to extremely low-frequency electromagnetic fields has been suggested to increase the risk for brain tumors. However, in our overview of studies on that topic, we concluded that no consistent association could be found.[12] In the present investigation, no association was found with occupations with potential exposure to electromagnetic fields, such as electrician, electronics work, lineman, or telecommunications work. Nor did use of a video display unit increase the risk.

Some studies have suggested an association with exposure to certain pesticides.[1,13] This was not found in this study. Regarding aspartame, it is difficult to assess total exposure, since it occurs in different types of food, such as beverages, ice cream, cakes, and sweets. However, the highest per capita exposure is from low-calorie drinks, with an estimate of 45% in a Norwegian study.[5] Thus, we assessed only intake of such beverages. For malignant brain tumors, an increased risk was found in the highest-exposure group. This was based on low numbers and must be interpreted with caution. Also, the cutoff dose for dividing the number of exposed controls into 2 groups with equal number was low (6864 centiliters) indicating possible underreporting of intake of low-calorie drinks. However, the meanage of cases and controls was 50 years, and consumption of low-calorie drinks is clearly a more common habit in young subjects. No increased risk was found in a US study on childhood brain tumor and aspartame consumption.[14]

During a mobile phone call, depending on the antenna, highest exposure occurs in the temporal, occipital, and temporoparietal lobes on the same side of the head used for the call. There is a rapid decline of the microwave dose in the brain, and the other side of the brain is only exposed to a low degree. An increased risk for brain tumors in the anatomic areas with highest exposure to microwaves from a cellular telephone has previously been reported from this investigation.[6] In that report, we displayed the results for each hemisphere separately. We have now combined the areas with highest exposure (temporal, occipital, and temporoparietal lobes), the remaining lobes with low exposure (frontal, parietal frontoparietal, and parieto-occipital), and also each hemisphere irrespective of left or right side of the brain. The OR was calculated for ipsilateral, contralateral, or both ipsilateral and contralateral (both sides reported by some subjects) exposure to microwaves from a mobile telephone. An increased risk was only found for ipsilateral exposure in the anatomic area with the highest microwave dose. In a multivariate analysis including other exposures with significantly increased risk, this result was further strengthened.

Obviously, this result was based on low number of exposed subjects and

must be interpreted with caution. However, the finding might be of biological relevance. Since patients do not usually have exact information of the anatomic area (lobe) of the tumor, recall bias is less likely to explain the results. All but 1 of these 13 patients had used the NMT system (analogue), and it should be noted that analogue telephones have at least a 3 times higher output power than digital telephones. In the 1980s, only the analogue system was used, and the digital system was introduced in the Swedish market in early 1990s; thus, tumor induction period might also be relevant. Because of the low numbers, it was not meaningful to calculate ORs according to tumor induction time or cumulative exposure in hours fo r high-exposure area of the brain. Other parts of the brain were also inc luded in multivariate analysis, but the results were similar to the univariate analysis.

**Acknowledgments**

This study was supported by grants from Cancer- och Allergifonden, the Swedish Medical Research Council, and Orebro Cancer Fund. Ms Irène Larsson and Ms Lena Akerlund participated in the data collection. Professor Kjell Hansson Mild gave advice on technical aspects of the use of cellular telephones.

**Table 1. Odds Ratios (ORs) and 95% Confidence Intervals (CI) for Ever Employment in Various Occupations.**

| Occupation | Cases/Controls | OR (95% CI) |
|---|---|---|
| Building worker | 15/27 | 1.09 (0.54-2.21) |
| Chemical industry | 9/4 | 4.10 (1.25-13.4) |
| Dressmaker | 6/6 | 1.89 (0.61-5.89) |
| Electrician | 1/12 | 0.16 (0.02-1.20) |
| Electronics work | 15/44 | 0.60 (0.32-1.14) |
| Engineer, technician | | |
| All | 18/42 | 0.80 (0.44-1.45) |
| Chemical work | 2/2 | 1.69 (0.23-12.2) |
| Electronics, telecommunications | 0/9 | . . . |
| Mechanical | 5/9 | 1.05 (0.35-3.16) |
| Technical, other | 7/6 | 2.41 (0.75-7.73) |
| Farmer | 14/35 | 0.68 (0.33-1.41) |
| Laboratory work | 10/6 | 3.21 (1.16-8.85) |
| Lineman | 1/7 | 0.23 (0.03-1.91) |
| Lumberjack | 13/28 | 0.84 (0.41-1.72) |
| Nurse | 5/7 | 1.27 (0.40-4.04) |
| Nurse assistant | 26/40 | 1.25 (0.72-2.17) |
| Painter | 5/16 | 0.60 (0.21-1.70) |
| Plastics work | 6/10 | 1.20 (0.44-3.30) |
| Physician | 3/1 | 6.00 (0.62-57.7) |

| | | |
|---|---|---|
| Radar work | 5/8 | 1.25 (0.41-3.82) |
| Sawmill worker | 4/13 | 0.58 (0.18-1.89) |
| Telecommunications work | 25/50 | 0.97 (0.58-1.60) |

**Table 2. Physicians' Duration of Work With Fluoroscopy at a Radiology Department**

| Sex | Age, y | Year of Exposure/ Duration of Exposure | Diagnosis (Year Diagnosis Made) |
|---|---|---|---|
| Female | 51 | 1968, 6 mo | Meningioma (1996) |
| Male | 52 | 1976, 3 mo | Acoustic neurinoma (1996) |
| Male | 56 | 1964-1995 | Oligodendroglioma (1995) |
| Male | 70 | No exposure | Control |

**Table 3. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Exposure to Different Agents**

| Agent | Cases/Controls | OR (95% CI) |
|---|---|---|
| Asbestos | 9/15 | 1.20 (0.52-2.74) |
| Aspartame* (in light beverage) | 30/45 | 1.24 (0.72-2.14) |
| < 6864 centiliter | 18/21 | 1.64 (0.80-3.38) |
| >/=3D 6864 centiliter | 12/22 | 1.02 (0.49-2.14) |
| Aspartame,* malignant tumors | 21/25 | 1.70 (0.84-3.44) |
| <6864 centiliter | 10/15 | 1.32 (0.52-3.36) |
| >/=3D 6864 centiliter | 11/8 | 2.66 (1.01-7.04) |
| Aspartame, benign tumors | 8/15 | 0.96 (0.36-2.54) |
| < 6864 centiliter | 7/5 | 2.93 (0.73-11.7) |
| >/=3D 6864 centiliter | 1/10 | 0.18 (0.02-1.49) |
| Cutting oils | 5/11 | 0.90 (0.30-2.69) |
| Exhaust (occupational) | 37/76 | 0.87 (0.54-1.39) |
| Fungicides | 0/3 | . . . |
| Glue | 29/43 | 1.37 (0.80-2.38) |
| Herbicides | 13/23 | 1.02 (0.49-2.12) |
| Phenoxyacetic acids | 3/9 | 0.46 (0.10-2.18) |
| Other | 7/7 | 1.64 (0.57-4.75) |
| Impregnating agents | 28/49 | 1.13 (0.69-1.85) |
| Insecticides | 11/28 | 0.74 (0.36-1.49) |
| Oils | 4/5 | 1.60 (0.43-5.96) |
| Organic solvents | 91/160 | 1.15 (0.79-1.68) |
| Smoking, ever | 117/218 | 1.02 (0.72-1.45) |
| Current smoker | 47/94 | 0.94 (0.61-1.46) |
| Ex-smoker | 70/124 | 1.09 (0.72-1.64) |
| Video display unit | 114/196 | 1.28 (0.88-1.86) |
| < 601 Working days | 63/101 | 1.36 (0.88-2.08) |
| >/=3D601 Working days | 51/95 | 1.20 (0.77-1.87) |
| Occupational use | 99/177 | 1.12 (0.78-1.61) |
| Leisure time use | 53/95 | 1.11 (0.74-1.66) |

*Information on dose missing for 2 controls; histopathologic test results not available for 12 patients.

**Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Exposure to Cellular Telephone According to Tumor Localization in Relation to Ear (Side) Used for Cellular Telephone***

| | ORs (95% CIs) [Cases/Controls] | | |
|---|---|---|---|
| **Tumor Localization** | **Ipsilateral** | **Contralateral** | **Ipsilateral and Contralateral** |
| Brain, hemisphere | 1.07 (0.64-1.80) | 0.70 (0.39-1.24) | 1.35 (0.57-3.22) |
| | [34/59] | [20/54] | [10/12] |
| Frontal, frontoparietal, parietal, or parieto-occipital | 0.88 (0.45-1.74) | 0.57 (0.26-1.26) | 3.07 (0.89-10.6) |
| | [20/41] | [9/31] | [8/4] |
| Temporal, occipital or temporoparietal | 2.42 (0.97-6.05) | 1.06 (0.42-2.70) | 0.65 (0.13-3.33) |
| | [13/12] | [10/19] | [2/6] |

*Latency period of more than 1 year. Note that no lobe was applicable for 23 cases.

**Table 5. Odds Ratio (ORs) and 95% Confidence Intervals (CIs) for Exposures in a Multivariate Analysis**

| | **Univariate OR (95% CI)** | **Multivariate OR (95% CI)** |
|---|---|---|
| Cellular telephone | | |
| (temporal, occipital, or temporoparietal lobe) | | |
| Ipsilateral exposure | 2.42 (0.97-6.05) | 2.62 (1.02-6.71) |
| Contralateral exposure | 1.06 (0.42-2.70) | 0.97 (0.36-2.59) |
| Ipsilateral/contralateral exposure | 0.65 (0.13-3.33) | 0.71 (0.14-3.68) |
| Laboratory work | 3.21 (1.16-8.85) | 8.81 (0.96-80.7) |
| Medical diagnostic x-ray investigations, head and neck | 1.64 (1.04-2.58) | 1.66 (0.75-3.65) |

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