Geothermal areas and cancer

Aðalbjörg Kristbjörnsdóttir

Thesis for the degree of Philosophiae Doctor

Desember 2016

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Jarðhiti og krabbamein

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Ágrip

Inngangur: Erlendar rannsóknir hafa sýnt að búseta á jarðhita og eldfjalla svæðum tengist hærri tíðni ákveðinna tegunda krabbameina. Markmiðið var að rannsaka tengsl búsetu á jarðhitasvæðum og tíðni krabbameina á Íslandi.

Efniviður og aðferðir: Í fjórum lýðgrunduðum hóprannsóknum var einstaklingum úr manntali 1981 fylgt eftir til loka árs 2013. Eftirfylgnin fór fram í Krabbameinsskrá og Dánarmeinaskrá. Viðbótarupplýsingar voru fengnar úr gagnagrunnum um reykinga venjur og barneignir. Útsettur hópur og samanburðar hópar voru skilgreindir samkvæmt sveitarfélagsnúmerum, eftir aldri hitaveitna og aldri berggrunns. Notuð var lifunargreining og áhættuhlutfall reiknað með 95% öryggismörkum með fjölþátta greiningu.

Niðurstöður: Í rannsóknunum, með nærri 33 ára eftirfylgni og um 1000 krabbameins tilfellum á jarðhitasvæðum, fannst marktækt hærri tíðni vegna allra krabbameina saman, krabbameina í briskirtli, brjóstum, blöðruhálskirtli, nýrum, eitil- og blóðmyndandi vefjum, eitilæxlum öðrum en Hodgkins meinum og grunnfrumukrabbamein í húð, á jarðhitasvæðum heldur en á samanburðarsvæðum. Í dánarmeinarannsókn var aukin áhætta á að deyja vegna krabbameina í brjóstum, blöðruhálskirtli, nýrum og eitilæxlum öðrum en Hodgkins meinum, og vegna sjálfsvíga og inflúensu. Krabbameinstíðnin tengdist lengd búsetu, og einnig var krabbameinstíðnin hærri því meiri sem jarðhitavirkin var og hitaveiturnar voru eldri. Auk þessa var krabbameinstíðnin hærri þegar tekið var tillit til 5 ára hugsanlegs framleiðslutíma krabbameinanna.

Ályktun: Ekki er vitað hver er orsökin fyrir hárri tíðni krabbameina á jarðhitasvæðunum á grunni þessara vistfræðilegu rannsókna. Frekari rannsókna er þörf á efna- og eðlisfræðilegum þáttum jarðhitavatns og umhverfisþátta á jarðhitasvæðum, til að athuga hvort finnast þekktir og/eða óþekktir krabbameinsvaldar sem gætu skýrt þessa háu krabbameinstíðni.

Lykilorð: Jarðhitasvæði, Eldfjallasvæði, Brjósta krabbamein, Blöðruhálskirtils krabbamein, Grunnfrumu krabbamein í húð (BCC).

Abstract

Background and aims: Previous studies in geothermal and volcanic areas have shown high risk of certain types of cancers. The aim was to study the association between residence in geothermal areas and the incidence and mortality of cancer in Iceland.

Material and Methods: Studies I - IV are all population-based cohort studies. Records for individuals aged 5-64 years were obtained from the 1981 census, and they were followed through the years 1981-2013. A personal identifier was used in record linkage with nation-wide emigration, cause-of-death, and cancer registries. The exposed and reference populations were defined according to community codes, different ages of hot water supply systems, and age of bedrock. Hazard ratio, 95% confidence intervals stratified with and without cumulative years of residence were estimated in Cox-model, and different covariates were taken into account.

Result: In these studies, with 33 years of follow-up, and nearly 1000 cancer cases, a high incidence was found in the population of the geothermal areas in comparison with the reference populations for all cancers combined, pancreatic cancer, breast cancer, prostate cancer, kidney cancer, combined cancers of the lymphoid and haematopoietic tissue, non-Hodgkin lymphoma and basal cell carcinoma of the skin. In the mortality study, high mortality for breast cancer, prostate cancer, kidney cancer, and non-Hodgkin lymphoma, in addition to high mortality for suicide and influenza were found in the populations of geothermal areas compared with the reference populations. The cumulative years of residence increased the risk, and dose response relation was found through the degree of volcanic/geothermal activity. Requiring five years latency yielded a higher hazard ratio.

Conclusion: The result indicates high cancer risk in geothermal areas. The cause for this high incidence is not known from these ecological studies. Further studies are needed on the chemical and physical content of the geothermal water and the ambient air of the areas to detect recognized or new carcinogens.

Keywords: Geothermal area, Volcanic area, Breast cancer, Prostate cancer, Basal Cell Carcinoma (BCC).

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Last but not least, I wish to thank my family. Their love and support provided me the energy to attain my studies.

This thesis is dedicated to all people who have been diagnosed with cancer.

Contents

List of abbreviations

ANCR	Association of the Nordic Cancer Registries
As	Arsenic
BCC	Basal cell carcinoma
Cd	Cadmium
CI	Confidence Interval
CLL	Chronic lymphocytic leukaemia
CO_2	Carbon dioxide
Cr	Chromium
H_2	Hydrogen
H_2S	Hydrogen sulphide
H_2SO_4	Sulphuric acid
HCl	Hydrogen chloride
HF	Hydrogen fluoride
Hg	Mercury
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICD	International classification of disease
ICR	Icelandic Cancer Registry
IQR	Inter quartile range
Mn	Manganese
NORDCAN	Nordic Cancer data base
Pb	Lead
Pd	Palladium
Rn	Radon
SD	Standard deviation
SO_2	Sulfur dioxide
Tl	Thallium
U	Uranium
V	Vanadium
W	Tungsten
WHO	World Health Organization

List of figures

List of tables

List of original papers

This thesis is based on the following original publications, which are referred to in the text by Study I to Study IV:

I. Kristbjornsdottir A, Rafnsson V. (2012). Incidence of cancer among residents of high-temperature geothermal areas in Iceland: A census based study 1981 to 2010. Environmental Health, 11, 73. PMID: 23025471. doi.org/10.1186/1476-069X-11-73.

II. Kristbjornsdottir A, Rafnsson V. (2013). Cancer incidence among population utilizing geothermal hot water: A census-based cohort study. Int J Cancer, 133(12), 2944-2952. PMID: 23733434. doi.org/10.1002/ijc.28298.

III. Kristbjornsdottir A, Rafnsson V. (2015). Cancer mortality and other causes of death in users of geothermal hot water. Acta Oncologica, 54(1), 115-123. PMID: 24909377. doi.org/10.3109/0284186X.2014.923113.

IV. Kristbjornsdottir A, Aspelund T, Rafnsson V (2016) Association of Cancer Incidence and Duration of Residence in Geothermal Heating Area in Iceland: An Extended Follow-Up. PLoS ONE 11(5): e0155922. doi:10.1371/journal.pone.0155922.

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Declaration of contribution

Study I: The candidate Adalbjorg Kristbjornsdottir (AK) suggested the study and designed the study with supervisor Vilhjalmur Rafnsson (VR). Both authors were responsible for collecting data records from relevant institutions. The candidate prepared the data and analyzed the data in co-operation with a statistician Örn Ólafsson and wrote the paper in collaboration with supervisor and co-author (VR). Both authors approved and work on the final version.

Studies II and III: AK and VR designed the studies. Both authors were responsible for collecting data records from relevant institutions. AK prepared the data and analyzed the data and wrote the papers in collaboration with co-author VR. Both authors approved and work on the final versions.

Study IV: AK and VR designed the study. AK and VR were responsible for collecting data records from relevant institutions. AK prepared the data and analyzed the data and wrote the paper in collaboration with co-authors, VR and Thor Aspelund. All authors approved and work on the final version.

1 Introduction

Environmental pollution and its impact on human health have been considered a serious problem in active volcanic areas and millions of people globally live within those areas (1, 2).

Research in volcanic air pollution hazards has mainly concerned the acute toxic effects of gas or ash emission on people exposed near active vents. However, through the centuries, volcanic eruptions in Iceland have now and then emitted ash and gases that have been carried downwind to mainland Europe. Historically, such events have been associated with climate change and higher mortality in England and elsewhere (3).

1.1 Pollution in volcanic and geothermal area

During eruption and post-eruptive phases, volcanoes release numerous hazardous contaminants, including toxic gases and heavy metals (4). People living in the close vicinity of the volcano are usually those who suffer most in cases of eruption (5).

People living on volcanic ground may experience long-term low-level exposure to various toxic ground gas emissions for example, carbon dioxide (CO_2), hydrogen sulphide (H_2S), radon (Rn), sulphur dioxide (SO_2), sulphuric acid (H_2SO_4), hydrogen chloride (HCl), and hydrogen fluoride (HF), which are considered to pose chronic health hazards (6-8). Several other low-dose exposures have been mentioned. Among them, arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg) manganese (Mn), palladium (Pd), thallium (TI), uranium (U), vanadium (V) and tungsten (W) (4, 9, 10) and naturally occurring radioactive material (NORM) have been found in gas, scale and geothermal water emission (11-14).

Unlike emissions of hazardous air pollutants during eruptions, ground gas emissions from geothermal fields are continuous and communities in these areas may be chronically exposed to elevated gas concentrations, albeit at much lower levels. The ground gas emission in geothermal areas is a hazard that is characterised by the migration of gases from deep magma bodies or hydrothermal systems towards the surface and through the soil, to be emitted into the air. The main components of the gas emissions from the geothermal fields and fumaroles, and in the geothermal hot water in Iceland are CO_2,

H_2S, SO_2, and hydrogen (H_2). The information available from Icelandic settings indicates the presence of traces of hazardous elements in the geothermal water including As, Hg, and Rn, i.e. in low quantities, but in varying concentrations (15-18), and NORM accumulating in scales and sludge tanks from U-238 decay chain have been recently found in geothermal power plants in Iceland (19, 20).

1.2 The Icelandic Context

Iceland belongs to the Nordic countries and these countries are known for their equal-access health care systems for all citizens.

In the Nordic countries population-based registries of cancer have been kept for decades and the Association of the Nordic Cancer Registries (ANRC) is the cooperative organ for the national registries of Denmark, Finland, Iceland, Norway and Sweden (21), with a history back to the year 1908 (22). The cancer patterns in these countries have the characteristics of developed countries; however there are some differences between the incidences. The aim of the Nordic Cancer collaboration (NORDCAN) is to compare the cancer incidence rates in the countries and to use that comparison to identify factors that can explain the differences (23). In the year 2003, the NORDCAN project (database and program) was present in its full version and today, it disseminates detailed information and results on cancer incidence, mortality, prevalence and survival statistics for 50 major cancers in the Nordic countries (21, 23).

Iceland is geologically a young country, located in the North Atlantic Ocean, 65 00 N, 18 00 W (24) on the boundary between the North American and Eurasian tectonic plates. These two plates are moving apart at a rate of about 2 cm per year and Iceland is an anomalous part of the ridge where deep mantle material wells up and creates a hot spot of unusually great volcanic productivity and several geothermal fields (25, 26). As a result, earthquakes are frequent and more than 200 volcanoes are located within the main active volcanic zone stretching through the country from the southwest to the northeast. At least 20 high-temperature areas are located in this volcanic zone, which are directly linked to the active volcanic systems. About 250 separate low-temperature areas are found, mostly in the areas flanking the active volcanic zone, with over 600 hot springs (temperature over 20°C) (17, 26, 27).

1.2.1 The use of geothermal energy in Iceland

For over a century, geothermal hot water and steam have been used in Iceland for domestic heating, showering and bathing, in different industries and to generate electricity in power plants (26, 27). Through several decades, geothermal domestic heating became organised in different hot water supply systems and today, geothermal hot water, from deep-drilled wells is piped into power plants, industries, greenhouses and domestic homes, to be used for heating, laundry, bathing, showering and washing dishes. Geothermal water is not recommended as drinking water, and it tastes and smells foul like rotten egg, due to H_2S content. Approximately 90% of all houses and swimming pools are at present heated with geothermal water, and 12% of the electricity in Iceland is generated from geothermal power plants (28, 29).

1.3 Risk of cancer in geothermal and volcanic fields

Long-term studies on populations living on geothermal fields or in volcanic areas are scant. Cancer incidence and mortality due to cancer among these populations have so far been the subject of limited study and most of the studies have produced inconsistent results (9, 10, 30-36).

1.3.1 Thyroid cancer

In a Hawaiian study, Goodman et. al (30) showed that Hawaiian populations have some of the highest reported incidence rates for thyroid cancer in the world and the authors suggest that environmental influences are responsible for these unusually high rates (30).

In a study from Sicily, Pellegriti et al. (31) found that residents of Catania province, a volcanic region, have higher incidence of papillary thyroid cancer than other populations in Sicily, and concluded that the volcanic environment of Mt Etna may contribute to the increased risk of thyroid cancer. It is mentioned in the study that the concentration of Rn is elevated in the environment of the area. However, the authors were not able to conclude on the role of Rn exposure in the risk of thyroid cancer (31).

In an Icelandic study (32), Arnbjornsson et al. compared Icelandic populations with populations in other Nordic countries and found that thyroid cancer incidence was highest in Iceland. The authors suggested that the high rate of thyroid cancers was likely related to the volcanic activity in the country and to genetic factors (32). According to NORDCAN, in the years 2009-2014, the incidence of thyroid cancer in Iceland is still the highest among the Nordic countries (23).

In a recent study from Sicily, Malandrino et al. (10) compared individuals in the Mt. Etna volcanic area, Catania, with adjacent control areas and found increased risk of thyroid cancer. Authors mention that cadmium (Cd), mercury (Hg), manganese (Mn), palladium (Pd), thallium (TI), uranium (U), vanadium (V) and tungsten (W) in the water and atmosphere may have carcinogenic effects and suggest a relationship between the complex mixture of pollutants present in the Mt. Etna volcanic area and increased thyroid cancer (10).

1.3.2 Nasal and lung cancer

In the study of the populations of Rotorua, New Zealand, Bates et al. (33) found an increased risk of nasal and lung cancer among residents in a geothermal field, who were exposed to H_2S. The authors of this study concluded that the data on exposure were inadequate to permit conclusions on possible causal relationships between H_2S and Hg compounds and cancer incidence; however they considered that the increase in lung cancer was not explained by differences in smoking habits (33).

1.3.3 Breast cancer

In a study from the Azores, Portugal, Amaral et al. (9) compared two populations, one from an area with active manifestation of volcanism (Furnas) and another from an area with no volcanic activity for the past 3 million years (Santa Maria). In that study, female breast cancer was linked to residence on an actively degassing geothermal field and it was suggested that trace elements and high Rn exposure might play a role (9). These results are supported by a recent study, comparing cancer incidence in Azores and mainland Portugal (34).

1.3.4 Kaposi sarcoma

In a case-control study from Sicily, Pelser et al. (35) investigated whether residential exposures to volcanic soils or related soils were associated with the risk of classic Kaposi sarcoma in Sicily, and found an indication for that association (35).

1.3.5 Studies mentioning several cancer sites

In a study from Azores, Lacerda et al. (34) compared Azores populations with populations in mainland Portugal, and found significantly higher risk (standardized risk ratio) in both genders for all cancer sites combined and lymphoma. In men, increased risk of stomach, liver, pancreas, lung, prostate, bladder cancers, and leukaemia, and decreased colorectal cancer were found. In women cancer of breast, cervix uteri, corpus uteri, brain, nervous system and thyroid were increased (34). The authors concluded that smoking, long-term exposure to low doses of toxic gases (e.g. radon) derived from volcanic activity, and genetic susceptibility may contribute to this finding (34).

In a study from Sicily, Russo et. al. (36) found an increased risk of thyroid cancer and lymphatic leukaemia in men and women; Hodgkin lymphoma, stomach, and breast cancer were increased among women, and prostate cancer among men. The authors suggested that the increased risk of all cancers combined and for several tissue-specific types of cancer was a likely consequence of environmental pollution, and different cancer-specific carcinogens and different mechanisms may be responsible for the increased incidence of certain tumour types among residents in the volcanic area (36).

1.4 Carcinogenicity and IARC

The International Agency for Research on Cancer (IARC) was established with the objective of promoting international collaboration in cancer research. Expert groups, composed of members selected by IARC, have evaluated and classified different chemical and other agents based on all available research on whether they are carcinogenic to humans, and they have compiled lists of relevant cancer sites (37). The main focus has been on epidemiological studies. Sufficient evidence of carcinogenicity in humans means that a causal relationship has been concluded and that chance, bias, and confounding could be ruled out with reasonable confidence. Limited evidence of carcinogenicity in humans means that a causal relationship was credible but that chance, bias, or confounding could not be ruled out with reasonable confidence (38, 39).

In the IARC monographs on human carcinogenicity, the following categories are used (39):

Group 1: The agent is carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in human studies, or the agent may be placed in this category when evidence of carcinogenicity is less than sufficient but there is sufficient evidence of carcinogenicity in studies of experimental animals.

Group 2: This category includes agents for which evidence of carcinogenicity in human studies is almost sufficient and there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A or Group 2B.

Group 2A: The agent is probably carcinogenic to humans. This category is used when there is limited evidence of carcinogenicity in human studies and there is sufficient evidence of carcinogenicity in studies of experimental animals.

Group 2B: The agent is possibly carcinogenic to humans. This category is used for agents for which there is limited evidence of carcinogenicity in human studies and less than sufficient evidence of carcinogenicity in studies of experimental animals.

Group 3: The agent is not classifiable as to its carcinogenicity to humans. This category is used for agents for which the evidence of carcinogenicity is inadequate in humans and inadequate or limited in experimental animals.

Group 4: The agent is probably not carcinogenic to humans. This category is used for agents for which evidence suggests lack of carcinogenicity in humans and in experimental animals (39).

The IARC has through the years published evaluations on more than 100 cancer-causing agents in a series of 113 monographs (40, 41).

Examples of different agents, which have a possible association with volcanic or geothermal areas, have been extracted from different IARC monographs, and are shown in Table 1.

Table 1 Example of chemical elements and other agents that occur in small amounts in volcanic and geothermal settings and their IARC classifications as described in different IARC publications/volumes (37, 38, 41).

Agent	IARC Groups	Cancer sites with sufficient evidence in humans	Cancer sites with limited evidence in humans	IARC publications/volumes
Sulphuric acid (H_2SO_4)	1	Larynx	Lung	54, 100F
Arsenic (As) and inorganic As	1	Lung, skin, urinary bladder	Kidney, liver, prostate	23, Sup 7, 100C
Cadmium (Cd)	1	Lung	Kidney, prostate	58, 100C
Chromium (Cr), metallic	3			Sup 7, 49
Chromium (Cr) (III) compounds	3			49
Chromium (Cr) (VI)	1	Lung	Nasal cavity, paranasal sinus	Sup 7, 49, 100C
Lead (Pb)	2B			23, Sup 7
Lead (Pb), inorganic	2A		Stomach	Sup 7, 87
Lead compounds, organic	3			23, Sup 7, 87
Mercury (Hg) and inorganic Hg compounds	3			58
Alfa-particle emitters (Internalized radionuclide)	1	Lung, bone, mastoid process, paranasal sinus, gall bladder, liver.	Leukaemia, pancreas, prostate, other solid tumours.	78, 100D
Beta-particle emitters (Internalized radionuclide)	1	Leukaemia, solid cancers, thyroid.	Bone, soft tissue, digestive tract, leukaemia, salivary gland.	78, 100D
X- and gamma radiation	1	Bone, brain and central nervous system, breast (female), colon, kidney, leukaemia (excluding CLL), lung, oesophagus, salivary gland, skin (BCC), stomach, thyroid, urinary bladder, utero: multiple sites.	Liver, multiple myeloma, non-Hodgkin lymphoma, ovary, pancreas, prostate, rectum.	75; 100D

2 Aims

The overall aim of the thesis was to study whether residence and duration of residence, according to census and residence registries in geothermal areas, where inhabitants are exposed to geothermal emissions and the use of geothermal hot water, are associated with the risk of cancers.

2.1 Specific aims for studies

Specific aims for each study:

I. To evaluate whether residence in a high temperature geothermal area, where inhabitants are exposed to geothermal emissions and geothermal hot water, is associated with the risk of cancer.

II. To evaluate whether utilization of geothermal hot water, used for heating, bathing and washing, is associated with risk of cancer.

III. To evaluate cause-specific mortality, with special focus on cancer mortality, in geothermal heating areas where the population has been using geothermal hot water for space heating, bathing and washing for decades.

IV. To evaluate whether cumulative length of residence in a geothermal heating area, where the inhabitants are exposed through use of geothermal water for space heating, washing, and bathing, and through the ground gas emissions of geothermal fields in their vicinity, is associated with the risk of cancer.

3 Materials and methods

3.1 Source of data in the studies

These are population-based observational studies. The source of data was the 1981 National Census in Iceland, kept at Statistics Iceland (42, 43). In the census, each individual is filed under a personal identification number that is allocated at birth. The census includes information on age, gender, residence according to local community-code, education, and the type of dwelling.

The cohort for these studies was confined to people aged 5 to 65 years at the time of the census. The personal identification numbers were used in record linkage with the National Registry to obtain information, where applicable, on the date of emigration and with the National Cause-of-Death Registry to obtain information on vital status and, where applicable, the date and cause of death. These registries are kept at Statistics Iceland (43). In this way, it was possible to ascertain the vital and emigration status for the entire cohort. Thus it was possible to define person-years at risk for each individual. Those who emigrated could not be followed up regarding cancer status after the date of emigration, even in cases where they subsequently returned.

The personal identification numbers were also used in record linkage with the Icelandic Cancer Registry (ICR), which is a nationwide registry covering all cancer diagnosed in Iceland since 1955 (44, 45). The registry has virtually complete coverage and over 95% of the diagnoses are histologically confirmed. Presently the ICR uses ICD-03 for coding topography and morphology. The neoplasm locations are standardised to the ICD-10 by the ICR. Basal cell carcinoma (BCC) has been registered since 1981 in a special file at the ICR. BCC is not counted with the overall cancers in these studies and these cases are analysed separately. Through the record linkage we were able to establish whether each individual had cancer, and if so, to identify the cancer site, morphology, and date of diagnosis (44).

Lastly, the personal identification numbers were used in record linkage to find out duration of residence. Statistics Iceland (43) publishes annually the National Rosters of the population with personal identification numbers, addresses and community codes. Thus the National Rosters are registers of nation-wide residence. The information on the duration of residence was obtained from the available National Rosters for the years 1985, 1990, 1995, 2000 and 2004. If the location of an individual was in the same community in the census as in the National Rosters (1985, 1990 ….2004), it was assumed that the person had been resident in that community for the number of years between the census and the record of that person in the respective roster. In cases where the individual was not located in the same community in the roster 1985 as in the census 1981, the cumulative number of years of residence was estimated to be less than 5 years. In cases where the individual was located in the same community in the roster 1985 as in census 1981 but not in the same community in the roster 1990 (and so on through the rosters), the cumulative number of years of residence was estimated to be 5 years. The last residence category was estimated to have 24 or more cumulative years of residence. There were thus six categories of continuous cumulative residence: < 5 years, 5 to < 10 years, 10 to < 15 years, 15 to < 20 years, 20 to < 24 years, and ≥ 24 years, for the exposed population and for the reference populations.

The European shortlist (46) was used to define the causes of death and to standardise these to ICD-10 (47), except for the cancers, where the procedure described above for the ICR were applied.

3.2 Exposed population and unexposed populations

The names and codes of the communities in the 1981 census are shown in supporting information of Paper IV.

3.3 Study I

The four-digit community code in the census was used to identify the populations living in two communities located in high-temperature geothermal areas. The first of these communities is a small town in southern Iceland (Hveragerdi (8716)). The area surrounding Hveragerdi forms part of the Hengill central volcano and there are many hot springs, fumaroles and erupting geysers in the town. The second community is smaller and consists of a small town and agricultural district (Skutustadahreppur, Myvatn (6607)). This community is on the edge of the Krafla volcano. Fumes from geothermal activities are frequently seen in these communities. Both these communities are inland regions, unlike most communities in Iceland that are located in coastal regions. The geothermal field in these communities belongs to the high-temperature geothermal areas. The two comparison populations included residents of communities according to the four-digit codes other than these high-temperature geothermal areas. The first of these comparison populations included residents living well outside of the high-temperature zone, in what we call the cold reference area, where the bedrock is more than 3.3 million years old and the underground temperature at 1000 m depth is below 150°C (26, 27). The second comparison population included those living within the volcanic zone, where the bedrock dates from 0.8 million to 15 million years (26, 27), referred to here as the warm reference area. The people in the warm reference area may or may not be living in the vicinity of geothermal fields, as these are spread out over the whole country. However, the community codes did not allow for differentiation between those in the vicinity of geothermal fields and those who are not, so this population is considered to have a mixed exposure.

The population living in the capital Reykjavik and in the southwest peninsula of Reykjanes were excluded from these studies. The reason was that according to the ICR, the capital and southwest area has had higher cancer incidence than other parts of the country for decades, a well-known phenomenon in cancer registries, sometimes called the capital effect (48, 49).

The geology with reference to age of the bedrock and volcanism in Iceland is shown in Figure 1 and the location of the exposed and reference areas are shown in Figure 2.

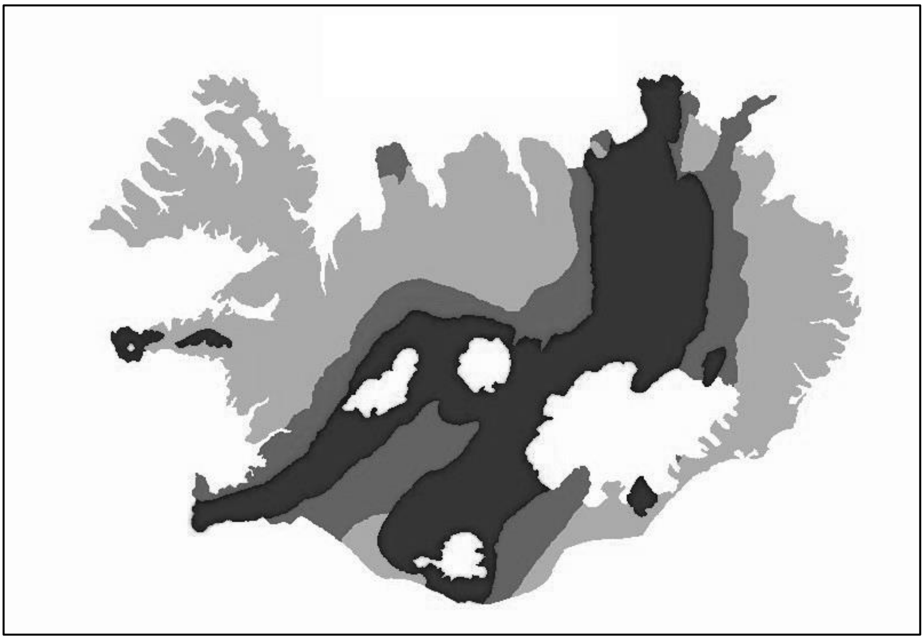

Figure 1 Geological map of Iceland. Dark grey area: age of bedrock less than 0.8 million years, grey area: age of bedrock 0.8-3.3 million years, light grey area: age of bedrock 3.3-15 million years, and white area: glaciers. Modified with permission from National Energy Authority.

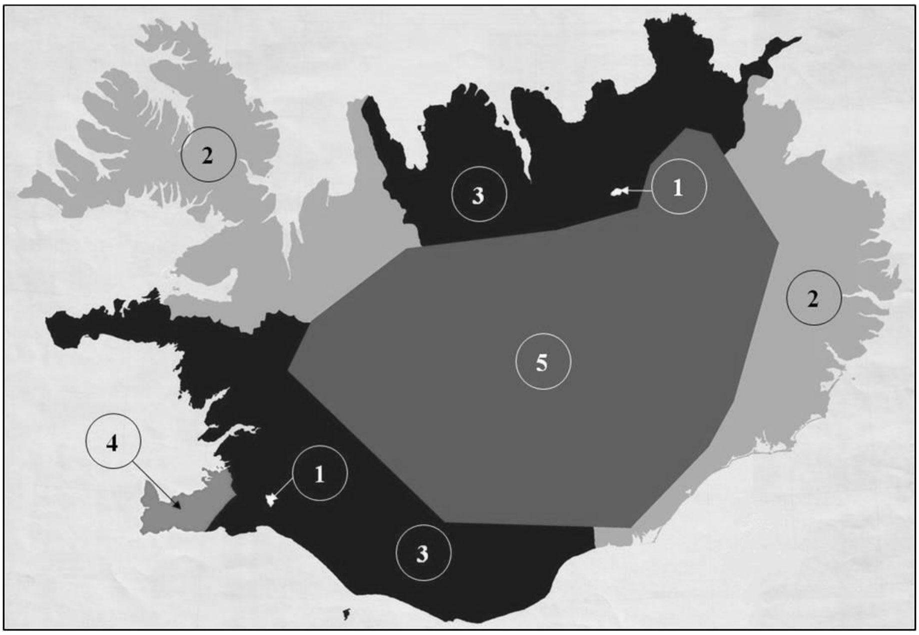

Figure 2 Map of Iceland, showing the study areas according to the community codes: 1) High-temperature geothermal area, 2) Cold reference area, 3) Warm reference area, 4) Capital and Reykjanes peninsula area, 5) Uninhabited area. Study I. Modified with permission from National Land Survey of Iceland.

3.4 Study II

The four-digit community code in the census was used to identify the populations living in communities with geothermal hot-water supply since 1972 or earlier, according to an overview of geothermal primary energy production for electricity generation and heating (28). In these communities the hot water has been used for domestic heating, laundry, bathing, showering and washing dishes. The hot water is not recommended as drinking water. Included in this group of communities, here called hot-water supply areas, are two small towns, Selfoss (8100), and Husavik (6100), and smaller rural districts, Reykjahreppur (6610), Laugardalshreppur (8712), Biskupstungnahreppur (8711), Hrunamannahreppur (8710) and Skeidahreppur (8708), and they are all located within the volcanic zone in the middle of the country, where age of bedrock is less than 3.3 million years old (26, 27). The exposed populations in Study I are excluded from this study.

The two comparison populations, classified according to the community codes in the census, included residents of communities other than the hot-water supply areas identified above. The first of these comparison populations was the same as in Study I, located in what we call the cold reference area. The second comparison population included that of the warm reference area in Study I who did not have hot water supply as early as 1972 or were located on bedrock dated from 0.8 to 15 million years. The population of the warm reference area, compared with the Study I, is reduced in size by the population of the hot-water supply areas.

As in Study I, the population living in the capital Reykjavik and in the southwest peninsula of Reykjanes was excluded from this study.

The geology and the location of the areas are shown in Figure 1 and Figure 3.

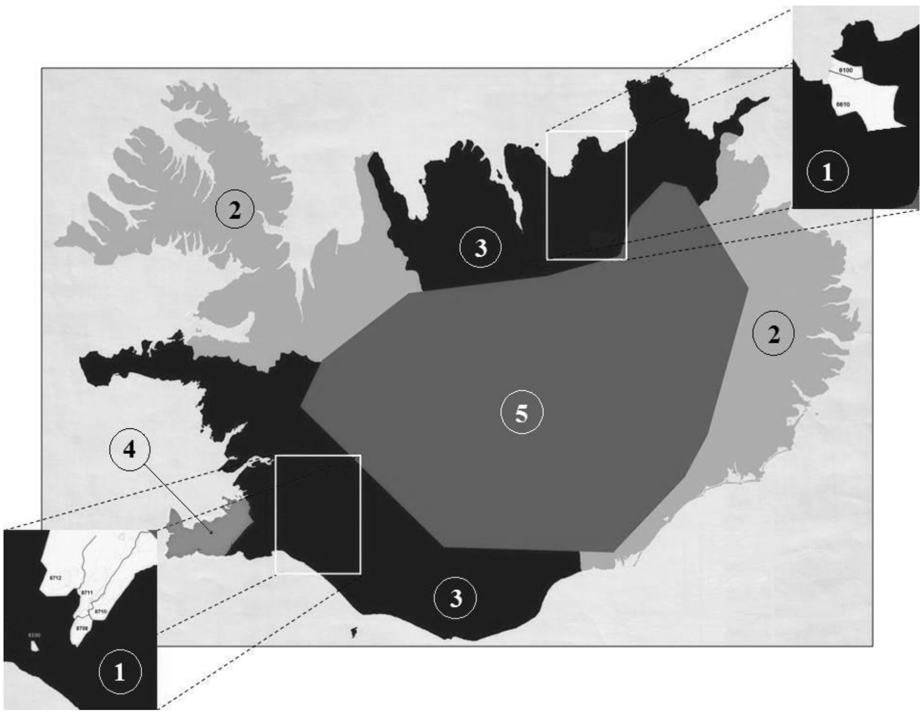

Figure 3 Map of Iceland showing the study areas: 1) Hot water supply areas are shown in two enlarged parts with community codes, 2) Cold reference area, 3) Warm reference area, 4) Capital and Reykjanes peninsula area, and 5) Uninhabited area. Study II. Modified with permission from National Land Survey of Iceland.

3.5 Study III

The four-digit community code in the census was used to identify the populations living in communities with geothermal heating since 1972 or earlier, according to an overview of geothermal primary energy production (28). In these communities, the hot water has been used for domestic heating, laundry, bathing, showering, and washing dishes, and in spas and swimming pools, but not recommended as drinking water. These are the exposed areas dealt with in Study I and Study II combined, here called geothermal heating areas. They included three small towns; two of these were inland, Selfoss (8100) and Hveragerdi (8716), and one was coastal, Husavik (6100), and six rural districts, Reykjahreppur (6610), Skutustadahreppur (6607), Laugardalshreppur (8712), Biskupstungnahreppur (8711), Hrunamannahreppur (8710), and Skeidahreppur (8708), all located within the volcanic zone in the middle of the country, where the bedrock is less than 3.3 million years old (26, 27). The two comparison populations, the cold reference area and warm reference area were the same as in Study II.

As in Studies I and II, the population living in the capital Reykjavik and in the southwest peninsula of Reykjanes was excluded from this study

The geology and the location of the areas are shown in Figure 1 and Figure 4.

Figure 4 Map of Iceland showing the study areas: 1) Geothermal heating areas, where geothermal district heating has been used since before 1972 are shown in two enlarged parts with community codes, 2) Cold reference area, 3) Warm reference area, 4) Capital and Reykjanes peninsula area, and 5) Uninhabited area. Studies III and IV. Modified with permission from National Land Survey of Iceland.

3.6 Study IV

The populations living in exposed areas and in reference areas are the same as in Study III.

As in Studies I to IV, the population living in the capital Reykjavik and in the southwest peninsula of Reykjanes was excluded from this study.

The geology and the location of these areas are shown in Figure 1 and Figure 4.

3.7 Follow-up - Person-time calculation

Study I and Study II

The follow-up started at the day of the census, 31 January 1981, and ended at the date of emigration, or the date of death, or the date of diagnosis of first cancer, or 31 December 2010 (the end of the follow-up period), whichever occurred first.

Study III

The follow-up started on the day of the census, 31 January 1981, and continued to the date of emigration, or the date of death, or 31 December 2009 (the end of the follow-up period), whichever occurred first.

Study IV

The follow-up started at the day of the census, 31 January 1981, and continued to the date of emigration, or the date of death, or the date of diagnosis of first cancer, or 31 December 2013 (the end of the follow-up period), whichever occurred first. Immortal person-time was taken into consideration, and excluded, which means that from follow-up time allocated to a specific exposure category, we excluded time during which the exposure-category definition was being met, according to Rothman and Greenland (50).

3.8 Covariate Assessment

Information on potential confounders was obtained from census 1981 i.e. age, gender, education (basic, medium, and higher education), and the type of residence (single family home and other type of dwelling), and these data were on an individual level.

3.8.1 Smoking

Information on smoking was not collected in the census and thus not available on an individual level. Since 1985, the Public Health Institute of Iceland has collected results from annual surveys on smoking habits among random samples of the population according to gender and postal codes (51).

Raw data on smoking surveys during 1991 to 1995 were obtained from the institute for the purpose of these studies. The postal codes were translated to community areas to fit into the community codes in the census and rates for never-smokers were calculated for each community and gender. These estimated never-smoker rates were assumed for inhabitants of the study areas, and allocated to the individuals of the respective communities regardless of age, but broken down by gender.

3.8.2 Reproductive factor

The age of women at first birth is the most important possible confounder in breast cancer studies of this design (52). Information on reproductive factors was not available from the census. However, data was obtained from Statistics Iceland on the exact number of women per age at first birth for the years 1991–1995 broken down by community codes. The information provided the birth age history for the respective communities, albeit unknown on an individual basis. From this information, reproductive factor proportions were calculated for number of women who had given first birth before 25 years of age, divided by number of women who had given first birth at 25 years of age or older. These reproductive factor proportions were allocated to each woman regardless of age, and according to the communities' codes in the geothermal areas, cold reference area and warm reference area.

3.8.3 BRCA2

It has been stated that the variation in prevalence of mutation in the BRCA2 gene across the study populations might account for our results, and we used the method of Axelson and Steenland (53, 54) to evaluate the possible confounding due to this unmeasured genetic factor. Axelson and Steenland introduced their method for evaluating the potential confounding effect of smoking in occupational studies; however, the method has been widely used, for example to evaluate confounding due to reproductive factors for the risk of female breast cancer (55). Mutation in the BRCA2 gene has been studied in families with high risk of breast cancer in both females and males in Iceland (56). This mutation was detected in 0.6% of the population (based on a random sample), in 7.7% of female breast cancer cases, and in 40% of males with breast cancer. The total 38 cases of males with breast cancer in the census 1981 (N=184 114, followed from 1981 to 2013), was used to calculate the prevalence of those with and without the mutation in the BRCA2 gene in the three study populations in Study IV, based on the number of male breast cancer patients: three in the geothermal heating area (n=7 511), nine in the warm (n=44 864), and five in the cold (n=22 431) reference areas. For the mutation in the BRCA2 gene, we assumed that the mutation was the only reason the population in the geothermal heating area had an elevated risk of breast cancer among females. We estimated the geothermal population expected female breast cancer incidence rate (53, 54) using the prevalence in the groups with and without the mutation, and known female breast cancer relative risk comparing those with and without the mutation. These risks were obtained from Thorlacius et al. (57) (modified to take age into account): the risk of breast cancer in a population of BRCA2 carriers as 7, relative to that of a population free from BRCA2 mutation set as 1. This incidence rate was compared with the expected female breast cancer incidence rate in the populations in the warm and cold reference areas, which had been estimated using analogous fractions, and corresponding female breast cancer risk of these populations.

3.9 Statistical Analyses

The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI) for all cancers and selected cancer sites in time-dependent analyses (58).

Gender was introduced as a dichotomous variable, and age as a continuous variable in years. Educational level (basic, medium and higher education), was introduced as a categorical variable according to the previous classification in a census study (59) with an additional two categories: those, unclassified for people under 20 years of age, who had not yet attained their full education level at the time of the census, and those with missing educational information, for individuals who did not indicate their education in the census. Type of residence, single-family house or other type of dwelling, was introduced as a dichotomous variable. Smoking was introduced as a continuous variable and reproductive factors were introduced as a continuous variable.

In the case of few outcomes (less than 3 cases in an area) the bootstrapping method was used for calculation of 95% CI. The bootstrap samples were generated by sampling with replacement 1000 times for each individual dataset (60).

The statistical analyses were performed using Microsoft Excel 2007 in studies I to IV, and PASW (SPSS) software, version 18.0, in study I to III (61) and, SPSS software, version 22.0 (62) in studies IV and STATA version 11 (63) in study I.

The National Bioethics Committee (VSNb2010060005/03.1) and the Data Protection Commission (2010060524ÞPJ/--) approved the studies.

4 Results

Iceland's population is homogenous Caucasian. Over the period the studies spanned, from 31 January 1981 to 31 December 2013, the population grew from 229 327 to 325 671 (43).

In the year 2015, Icelandic women and men had in the year 2015 the highest life expectancy in the Nordic countries (64). According to WHO statistics 2014, life expectancy for Icelandic women is 84.2 years and Icelandic men 81.2 (65).

In this thesis, data from Census 1981 were used. The number of individuals aged 5 to 64 years included in the census was 184 114, which represents 99.2% of this age group recorded in the National Registry (43). At the end of the follow-up on 31 December 2013, 10.9% of the populations had died, 17.6% had out-migrated, and 13.1% had been diagnosed with first cancer.

Around one-third of Icelanders can expect to be diagnosed with cancer during their lifetime and more than 50% of all cancer cases were diagnosed after the age of 65 years (44). The five-year relative survival for all cancer has more than doubled since the year 1964 (23) and cancer was the cause of 28 % of all deaths in Iceland in the year 2013 (44, 66).

4.1 The baseline characteristics and covariate assessment in the study populations

In the studies, a total of 74 068 individuals from the 1981 census was included, and at the end of the follow-up, on 31 January 2013, 62.7% of them were still alive, had not out-migrated, and were without cancer. During the study period, 10.3% of the populations had died, 15.1% had out-migrated, and 11.9% had been diagnosed with first cancer. A total of 8843 individuals (4702 men and 4141 women) were diagnosed with first cancer during the 33 years of the follow-up.

The baseline characteristics in the study populations according to census 1981 and covariate assessment from other available sources are shown in Table 2. The Kaplan-Meier estimates of the event-free proportion for all cancer sites combined in the geothermal heating area and cold reference area from Study IV are shown in Figure 5.

Table 2 Baseline characteristics of the study populations, data sources were census 1981[a], Directorate of Health [b], and Statistics Iceland [c].

	Geothermal area	Warm reference area	Cold reference area
Number of people [a]	N = 7511	N = 44 864	N = 22 431
Gender [a]			
Men	3893 (51.8)	23 305 (51.9)	11 929 (53.2)
Women	3618 (48.2)	21 559 (48.1)	10 502 (46.8)
Age, year [a]			
Mean ± SD	28.81 ± 16.35	28.65 ± 16.30	28.56 ± 16.20
Median, IQR (0.25 ; 0.75)	26 (15 ; 41)	26 (15 ; 40)	26 (15 ; 40)
Education [a]			
Basic education	1829 (24.3)	12 370 (27.6)	6565 (29.3)
Medium education	2088 (27.8)	11 754 (26.2)	5665 (25.3)
Higher education	622 (8.3)	3171 (7.1)	1428 (6.4)
Unclassified	2878 (38.3)	17 061 (38.0)	8481 (37.7)
Missing	94 (1.3)	508 (1.1)	292 (1.3)
Housing [a]			
Single family home	5730 (76.3)	29 236 (65.2)	17 343 (77.3)
Other type of residence	1781 (23.7)	15 628 (34.8)	5088 (22.7)
Never smoker % [b]			
Median	43.33	46.67	46.51
Range (lowest ; highest)	38.24 ; 54.86	31.82 ; 57.26	9.52 ; 57.78
Giving birth before 25 years of age % [c]			
Median	77.36	68.54	71.24
Range (lowest ; highest)	55.26 ; 86.96	61.94 ; 79.17	40.00 ;78.79

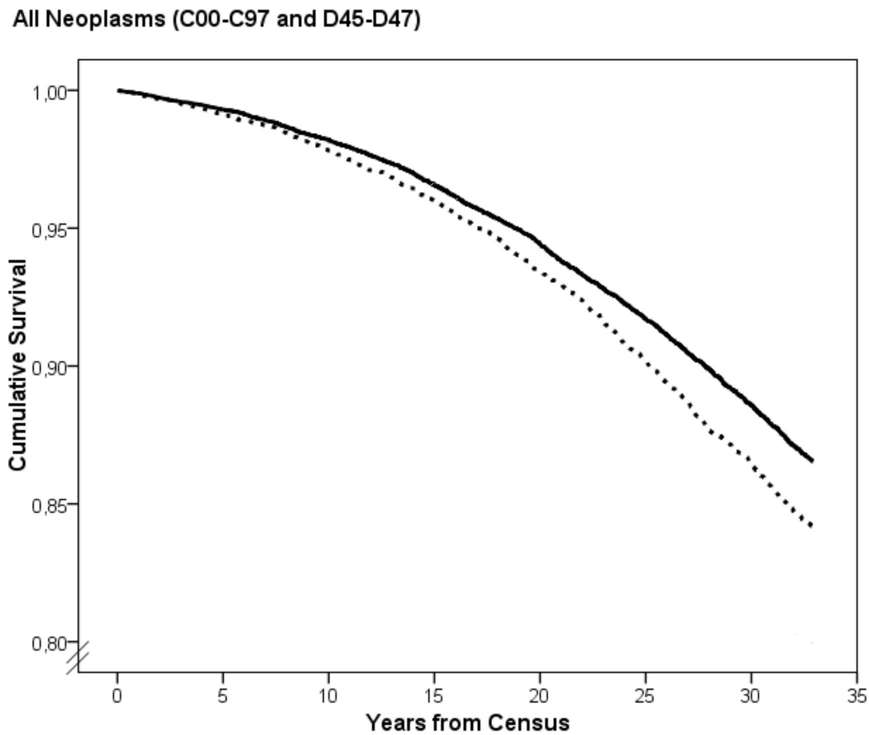

Figure 5 The Kaplan-Meier estimates of the event-free proportion for all cancers sites combined, in study areas in Study IV, from the date of census 1981 to the end of the year 2013. Dotted line: geothermal heating area, solid line: cold reference area.

4.2 Study I

In this study the number of individuals were 74 806 and altogether there were 1 901 786 person-years of follow-up. The average of follow-up was 24.9 years.

During the study period 184 individuals were diagnosed with first cancer in the high-temperature geothermal area (90 men and 94 women); 5314 (2798 men and 2516 women) in the warm reference area; and 2191 (1151 men and 1040 women) in the cold reference area.

Table 3 Number of all cancers and selected cancer sites, among men and women combined in the high-temperature geothermal area (n = 1497), and hazard ratio (HR), 95% confidence intervals (CI) in separated comparison with populations in warm (n = 50 878) and cold (n = 22 431) reference area, adjusted for age, gender, education, and type of housing. Study I. Statistically significant HR's are bolded.

	High-temperature geothermal areas	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	184	**1.16**	**1.00 to 1.34**	**1.22**	**1.05 to 1.42**
Pancreas (C25)	9	**2.57**	**1.30 to 5.07**	**2.85**	**1.39 to 5.86**
Bone (C40-C41)	2	3.56	0.83 to 15.27	**5.80**	**1.11 to 30.32***
Breast (C50)	31	**1.43**	**1.00 to 2.05**	**1.59**	**1.10 to 2.31**
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	18	1.53	0.95 to 2.46	**1.64**	**1.00 to 2.66**
Non-Hodgkin lymphoma (C82-C85)	12	**3.21**	**1.77 to 5.82**	**3.25**	**1.73 to 6.07**
Not included in all cancers					
Basal cell carcinoma of the skin	30	**1.37**	**0.95 to 1.97**	**1.61**	**1.10 to 2.35**

* 95% CI computed with bootstrap method were wide and included unity.

The adjusted HR and 95% CI were calculated for all cancers combined and selected cancer sites in Cox analyses. The comparison between the high-temperature geothermal area, warm reference area, and cold reference area, for all cancers and for selected cancer sites, where the 95% CI did not include unity are shown in Table 3.

The HRs for some other cancer sites were high but these were either based on few cases, or were followed by wide 95% CI, see Paper I. Separate analyses according to gender and age categories were calculated and shown in Paper I.

4.3 Study II

The number of individuals in the study was 73 309 and in total there were 1 866 079 person-years in the study. The average follow-up was 24.9 years. Over the study period, 673 individuals were diagnosed with first cancer in the exposed area (351 men and 322 women); 4641 (2447 men and 2194 women) in the warm reference area; and 2191 (1151 men and 1040 women) in the cold reference area.

Table 4 Number of all cancers and selected cancer sites, among men and women combined in the geothermal hot-water supply area (n = 6014), and hazard ratio (HR), 95% confidence intervals (CI) in separate comparison with populations in warm (n = 44 864), and cold (n = 22 461) reference areas, adjusted for age, gender, education, type of housing and smoking habits. Study II. Statistically significant HR's are bolded.

	Hot-water supply areas	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	673	**1.10**	**1.01–1.20**	**1.15**	**1.05–1.25**
Breast (C50)	112	**1.28**	**1.04–1.59**	**1.40**	**1.12–1.75**
Prostate (C61)	117	**1.48**	**1.21–1.82**	**1.61**	**1.29–2.00**
Kidney (C64-C66)	38	**1.51**	**1.05–2.18**	**1.64**	**1.11–2.41**
Brain and central nervous system (C70-C72, C75.1 and C75.3)	14	**0.56**	**0.32–0.98**	0.64	0.36–1.13
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	62	**1.34**	**1.01–1.78**	**1.45**	**1.08–1.95**
Not included in all cancers					
Basal cell carcinoma of the skin	110	**1.24**	**1.01–1.54**	**1.46**	**1.16–1.82**

The adjusted HR and 95% CI were calculated for all cancers combined and selected cancer sites in Cox analyses. The comparison between geothermal hot-water supply area, warm reference area, and cold reference area, for all cancers and for selected cancer sites, where the 95% CI did not included unity are shown in Table 4.

HRs for some other cancer sites were high but these were either based on few cases, or were followed by wide 95% CI, see Paper II. Separated analyses were done after dividing the individuals into gender, and age groups and taking the fertility rate into account as a covariate for breast cancer, as shown in Paper II.

4.4 Study III

In this study the number of individuals was 74 806 and in total there were 1 892 558 person-years of follow-up. The average of follow-up was 24.6 years.

The number of deaths during study period was 996 individuals in the exposed area (596 men and 400 women); 6038 (3629 men and 2409 women) in the warm reference area; and 3068 (1907 men and 1161 women) in the cold reference area.

Table 5 Number of selected causes of death, among men and women combined in geothermal heating area (n = 7511), and hazard ratio (HR), 95% confidence intervals (CI) in separate comparison with populations in warm (n = 44 864), and cold (n = 22 431) reference area, adjusted for age, gender, education, type of housing and smoking habits. Study III. Statistically significant HR's are bolded.

	Geothermal heating area	Warm reference area		Cold reference area	
Causes of death (ICD-10)	No. of deaths	HR	95%CI	HR	95%CI
Breast cancer (C50)	41	**1.48**	**1.03 – 2.12**	**1.53**	**1.04 – 2.24**
Prostate cancer (C61)	47	**1.88**	**1.33 – 2.66**	**1.74**	**1.21 – 2.52**
Kidney cancer (C64 – C66)	21	1.39	0.85 – 2.28	**1.78**	**1.03 – 3.07**
Non-Hodgkin lymphoma (C82-C85)	16	**1.96**	**1.09 – 3.55**	**2.01**	**1.05 – 3.84**
Endocrine, nutritional and metabolic diseases (E00 – E90)	10	0.58	0.30 – 1.13	**0.47**	**0.24 – 0.93**
Influenza (J10 – J11)	9	**3.77**	**1.58 – 8.99**	**3.36**	**1.32 – 8.58**
Suicide and intentional self-harm (X60 – X84)	41	**1.72**	**1.20 – 2.48**	**1.49**	**1.03 – 2.17**

The highest numbers of causes of death in the geothermal heating area were in following categories: malignant neoplasm (36.1%), diseases of the circulatory system (34.7%), diseases of the respiratory system (7.0%), accidents (5.5%), diseases of the nervous system and the sense organs (4.6%), suicide and intentional self-harm (4.1%).

Adjusted HRs and 95% CI were calculated for all causes of death combined and selected causes of death in Cox analysis, see Table 5 and Paper III.

The HRs for all causes of death and selected causes of death were in some cases high but these were based on few cases or followed by wide 95% CI, as shown in supplementary material in Paper III. Separated analyses were done according to gender, age categories, and breast cancer mortality with additional adjustment for age at first birth, as shown in Paper III.

4.5 Study IV

In this study the number of individuals was 74 806 and in total, the study included 955 604 person-years of follow-up, taking into account immortal person-years. The average follow-up was 32.92 years.

During the study period, the number of individuals diagnosed with first cancer was 988 in the geothermal heating area (517 men and 471 women); 5331 (2839 men and 2492 women) in the warm reference area; and 2524 (1346 men and 1178 women) in the cold reference area.

The adjusted HR and 95% CI were determined for all cancers combined and for selected cancer sites in Cox analysis. The HR for all cancers and selected cancer sites when geothermal heating areas were compared with warm and cold reference areas, where the 95% CI did not include unity, are shown in Table 6. Table 7 shows separated analyses taking duration of residence into consideration by stratification on the six categories of cumulative years of residence.

Table 6 Number of all cancers and selected cancer sites, among men and women combined in geothermal heating area (n = 7511), hazard ratio (HR), and 95% confidence intervals (CI) in separated comparisons with populations in warm (n = 44 864), and cold (n = 22 431) reference areas, adjusted for age, gender, education, type of housing and smoking habits. Study IV. Statistically significant HR's are bolded.

	Geothermal heating area	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	988	1.06	0.99 to 1.14	**1.17**	**1.09 to 1.26**
Pancreas (C25)	30	**1.50**	**0.99 to 2.27**	**1.87**	**1.18 to 2.95**
Breast (C50)	161	**1.23**	**1.03 to 1.46**	**1.42**	**1.18 to 1.72**
Prostate (C61)	172	**1.27**	**1.07 to 1.51**	**1.43**	**1.19 to 1.72**
Kidney (C64-C66)	49	1.21	0.88 to 1.67	**1.40**	**1.00 to 1.97**
Lymphoid and haematopoietic tissue (LH) (C81-C96 and D45-D47)	97	**1.30**	**1.03 to 1.64**	**1.49**	**1.17 to 1.91**
Non-Hodgkin lymphoma (NHL) (C82-C85)	39	**1.78**	**1.22 to 2.59**	**2.00**	**1.33 to 3.03**
NHL, diffuse (C83)	17	1.38	0.80 to 2.39	1.38	0.77 to 2.57
NHL, peripheral T-cells (C84)	6	**2.85**	**1.02 to 7.99**[b]	**3.84**	**1.11 to 13.31**[b]
NHL, unspecified (C85)	9	**5.13**	**1.99 to 13.21**[a]	**6.81**	**2.03 to 22.80**[a]
Myelodysplastic syndromes (MDS) (D46)	8	2.31	0.95 to 5.58	**4.02**	**1.38 to 11.71**[a]
MDS, unspecified (D46.9)	8	**3.41**	**1.32 to 8.83**[a]	**8.20**	**2.10 to 32.10**[a]
Other LH thrombocythemia (D47.3)	3	**11.43**	**1.64 to 79.80**[b]	8.61	0.85 to 86.98
Not included in all cancers					
Basal cell carcinoma of the skin	177	**1.22**	**1.03 to 1.45**	**1.54**	**1.28 to 1.85**

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity.

Table 7 Number of all cancers and selected cancer sites, among men and women combined in geothermal heating area (n = 7511), hazard ratio (HR), 95% and confidence intervals (CI) in separated comparison with populations in warm (n = 44 864), and cold (n = 22 431) reference areas, after taking the duration of residence into account by stratification on the six categories of cumulative years of residence, adjusted for age, gender, education, type of housing and smoking habits. Study IV. Statistically significant HR's are bolded.

	Geothermal heating area	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	988	**1.10**	**1.02 to 1.18**	**1.21**	**1.12 to 1.30**
Pancreas (C25)	30	**1.53**	**1.00 to 2.32**	**1.93**	**1.22 to 3.06**
Breast (C50)	161	**1.27**	**1.07 to 1.52**	**1.48**	**1.23 to 1.80**
Prostate (C61)	172	**1.32**	**1.11 to 1.57**	**1.47**	**1.22 to 1.77**
Kidney (C64-C66)	49	1.27	0.92 to 1.75	**1.46**	**1.03 to 2.05**
Lymphoid and haematopoietic tissue (LH) (C81-C96 and D45-D47)	97	**1.36**	**1.08 to 1.72**	**1.54**	**1.21 to 1.97**
Non-Hodgkin lymphoma (NHL) (C82-C85)	39	**1.90**	**1.30 to 2.77**	**2.08**	**1.38 to 3.15**
NHL, diffuse (C83)	17	1.48	0.85 to 2.57	1.45	0.80 to 2.62
NHL, peripheral T-cells (C84)	6	**2.91**	**1.04 to 8.19**[b]	**3.93**	**1.12 to 13.74**[a]
NHL, unspecified (C85)	9	**5.23**	**2.02 to 13.54**[a]	**6.75**	**2.01 to 22.64**[a]
Myelodysplastic syndromes (MDS) (D46)	8	**2.44**	**1.01 to 5.90**[b]	**4.07**	**1.39 to 11.93**[a]
MDS, unspecified (D46.9)	8	**3.70**	**1.42 to 9.64**[a]	**8.09**	**2.06 to 31.79**[a]
Other LH thrombocythemia (D47.3)	3	**12.72**	**1.80 to 89.74**[b]	7.53	0.74 to 76.48
Not included in all cancers					
Basal cell carcinoma of the skin	177	**1.28**	**1.08 to 1.52**	**1.62**	**1.35 to 1.94**

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity.

The HRs for many of the cancer sites, not shown in table 6 or table 7, were high, but the 95% CIs were wide and included unity, as shown in Paper IV. Separate analyses according to gender, age categories, breast cancer with additional adjustment for age at first birth, and categories of cumulative years of residence were also performed and are shown in Paper IV.

4.5.1 Study IV, application of five-year latency time

When applying five-year latency time, 372 individuals were diagnosed with first cancer in the geothermal heating area (189 men and 183 women); 1845 (984 men and 861 women) in warm reference area; and 959 (478 men and 481 women) in the cold reference area.

Table 8 Number of all cancers and selected cancer sites, among men and women combined in the geothermal heating area (n = 7511), and hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area (n = 44 864) and cold reference area (n = 22 431), applying five-year latency time, adjusted for age, gender, education, type of housing, and smoking habits. Study IV. Statistically significant HR's are bolded.

	Geothermal heating area	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	372	1.11	0.99 to 1.25	**1.19**	**1.06 to 1.35**
Pancreas (C25)	11	1.92	0.94 to 3.91	1.90	0.90 to 4.00
Breast (C50)	56	1.11	0.82 to 1.49	1.28	0.94 to 1.76
Prostate (C61)	57	1.15	0.85 to 1.54	1.31	0.96 to 1.79
Kidney (C64-C66)	16	1.03	0.59 to 1.78	1.17	0.66 to 2.10
Lymphoid and haematopoietic tissue (LH) (C81-C96 and D45-D47)	37	**1.49**	**1.02 to 2.17**	**1.64**	**1.10 to 2.44**
Non-Hodgkin lymphoma (NHL) (C82-C85)	17	**2.12**	**1.18 to 3.80**	**2.98**	**1.50 to 5.89**
NHL, diffuse (C83)	9	2.04	0.93 to 4.51	2.35	0.97 to 5.70
NHL, peripheral T-cells (C84)	4	**4.22**	**1.02 to 17.44**[b]	**8.77**	**1.27 to 60.56**[a]
NHL, unspecified (C85)	3	N	N	**12.38**	**1.12 to 137.26**[b]
Myelodysplastic syndromes (MDS) (D46)	7	**3.97**	**1.40 to 11.29**[a]	**11.30**	**2.25 to 56.67**[a]
MDS, unspecified (D46.9)	7	**6.48**	**2.01 to 20.93**[a]	**20.59**	**2.51 to 169.15**[a]
Other LH thrombocythemia (D47.3)	1	6.34	0.34 to 118.41	N	N
Not included in all cancers					
Basal cell carcinoma of the skin	74	1.06	0.82 to 1.37	**1.44**	**1.09 to 1.96**

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity. N = no cancer case in reference area.

Table 9 Number of all cancers and selected cancer sites, among men and women combined in the geothermal heating area (n = 7511), and hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in the warm reference area (n = 44 864) and the cold reference area (n = 22 431), after taking the duration of residence into account by stratification on the six categories of cumulative years of residence, applying five-years latency time, adjusted for age, gender, education, type of housing, and smoking habits. Study IV. Statistically significant HR's are bolded.

	Geothermal heating area	Warm reference area		Cold reference area	
Cancers (ICD-10)	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	372	**1.16**	**1.03 to 1.30**	**1.22**	**1.08 to 1.37**
Pancreas (C25)	11	**2.11**	**1.03 to 4.34**	2.01	0.95 to 4.25
Breast (C50)	56	1.14	0.85 to 1.54	1.29	0.94 to 1.76
Prostate (C61)	57	1.21	0.90 to 1.63	1.35	0.98 to 1.85
Kidney (C64-C66)	16	1.06	0.61 to 1.84	1.18	0.66 to 2.10
Lymphoid and haematopoietic tissue (LH) (C81-C96 and D45-D47)	37	**1.61**	**1.10 to 2.36**	**1.70**	**1.14 to 2.55**
Non-Hodgkin lymphoma (NHL) (C82-C85)	17	**2.30**	**1.27 to 4.14**	**3.02**	**1.52 to 6.00**
NHL, diffuse (C83)	9	**2.27**	**1.02 to 5.05**[b]	**2.51**	**1.02 to 6.14**[a]
NHL, peripheral T-cells (C84)	4	**4.24**	**1.02 to 17.64**[b]	**8.93**	**1.25 to 63.69**[a]
NHL, unspecified (C85)	3	N	N	10.26	0.96 to 108.93
Myelodysplastic syndromes (MDS) (D46)	7	**4.17**	**1.46 to 11.94**[a]	**11.46**	**2.27 to 57.80**[a]
MDS, unspecified (D46.9)	7	**7.18**	**2.19 to 23.52**[a]	**20.74**	**2.50 to 171.80**[a]
Other LH thrombocythemia (D47.3)	1	8.68	0.44 to 170.13	N	N
Not included in all cancers					
Basal cell carcinoma of the skin	74	1.11	0.86 to 1.44	**1.48**	**1.12 to 1.96**

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity. N = no cancer case in reference area.

The adjusted HR and 95% CI were analysed with the requirement of five-year latency time, and these are shown for all cancers combined and selected cancer sites in Table 8, and in Table 9, stratified with six categories of cumulative years of residence. When applying five-year latency time, the size of the data is reduced, which generally results in wider 95% CI. However, the HRs are in most cases higher than in the analyses without latency application.

The HRs for many of the cancer sites, not shown in table 8 or table 9, were high, but the 95% CIs were wide and included unity, as shown in Paper IV. Separate analyses according to gender, age categories, breast cancer with additional adjustment for age at first birth, and with application of five-year latency time, and categories of cumulative years of residence were also performed and are shown in Paper IV.

4.5.2 BRCA2

Using the relative risk from the study of Thorlacius et al. (56), and the estimated prevalence of those with and without the mutation of the BRCA2 gene, the incidence of female breast cancer in the population of the geothermal heating area were 106.96, contrasted with the value of 103.48 in the population of the warm reference areas, and 103.90 in the population of the cold reference areas. The predictive value (53, 54), in the comparison of geothermal heating area versus warm reference area was 1.03, and for the geothermal heating area versus the cold reference area, 1.03. In both cases, the predictive value of 3% increase was obtained.

5 Discussion

5.1 Main findings (Studies I, II, IV)

In these population-based cohort studies, with almost 33 years of follow-up and with nearly a thousand cancer cases and nearly a thousand deaths in the geothermal areas, we found higher risk for all cancers combined, pancreatic cancer, breast cancer, prostate cancer, kidney cancer, combined cancers of the lymphoid and haematopoietic tissue, NHL, MDS, and BCC of the skin in comparison with the warm reference area and the cold reference area. Higher mortality risk in breast cancer, prostate cancers, and non-Hodgkin lymphoma shows that the cancers found are not confined to types with good prognosis, but also include fatal cancers.

The dose-response association was found through the degree of volcanic/geothermal activity, as the risk for these cancer sites mentioned above was higher in geothermal areas in comparison with the cold reference area than with the warm reference area.

When taking cumulative years of residence in the areas into consideration, the risk for the above-mentioned cancer sites was generally higher compared with the risk when length of residence was not accounted for, again in a dose-response manner of relationship.

When five-year latency time was applied, the HRs for some cancer sites was higher and included unity, compared with the analysis without five-year latency time.

In the studies, it was possible to adjust on an individual basis for age, gender, social variables such as type of housing and education, and on a community level for estimates of smoking and age at first birth.

5.1.1 Pancreatic cancer

There was a high incidence of pancreatic cancer in the total exposed cohort that was statistically significant among men and non-significant among women; male gender is one of the risk factors for pancreatic cancer. Other external risk factors for this malignancy are smoking and, with limited evidence, consumption of alcoholic beverages and red meat, and human exposure to carcinogenic agents such as Thorium-232, and X-rays and gamma-radiation (41).

In our studies, the smoking habits is not known on an individual basis, but information on smoking in these populations is accessible from the annual surveys of the Public Health Institute of Iceland (51) from the year 1989 to 2010. These data show that the number of smokers has been declining from 31.0% to 14.2% in the population over the period, and the number of smokers in the capital area and in the rest of the country has been similar for decades, so smoking habits are not likely to be a confounder. Supporting this view is the fact that the lung cancer risk was not statistically increased in the exposed cohort.

There is no obvious connection between the geothermal area pollution and pancreatic cancer. The carcinogenic effect of Rn has in most of the studies been related to lung cancer. However, in a collaborative analysis of 11 studies of Rn-exposed underground miners, Darby et al. (67) found an O/E of 1.05, 95% CI 0.85 to 1.29, for pancreatic cancer mortality, which was significantly related to cumulative exposure (67). In the conclusion of that study, this relation was dismissed, despite the fact that pancreatic cancer is a deadly cancer and therefore more suitable for a mortality study than cancers with better prognosis.

In an ecological study in Florida, Lin-Mares et al. (68) found that exposure to As contaminated drinking water wells may be associated with an increased risk of pancreatic cancer. Further studies were needed to confirm this finding, preferably case-control studies (68).

5.1.2 Breast cancer

The result of all studies in this thesis showed high incidence and high mortality for breast cancer in the exposed cohorts. This is consistent with the higher incidence of breast cancer among the population in the geothermal area of Furnas, Azores than in the non-geothermal area (9). The authors of that study concluded that the increased risk of breast cancer may be partially explained by the gas emission, trace elements and Rn exposure (9). The

Furnas study is supported by a recent study, where cancer incidence in Azores is compared with mainland Portugal (34).

The present studies also show consistent results with a recently published study indicating higher incidence of breast cancer among the population in Catania, the area with highest volcanic activity in Sicily, Italy, compared with areas with less volcanic activity (36). The authors conclude that increased risk of all cancers and for several tissue-specific types of cancer was a likely consequence of non-anthropogenic environmental pollution, and different cancer-specific carcinogens and mechanisms may be responsible for the higher incidence of certain tumour types among residents in the volcanic area (36). Besides the Portuguese and Sicilian studies (9, 36), there is scant literature on the association of exposure to Rn and cancer among women: there were no female workers in the mining populations (69) and the case-control studies on residential exposure to Rn did not deal with breast cancer.

A study from Furnas, Azores, showed evidence of DNA damage in residents of active volcanic areas in comparison with an area without manifestations of volcanic activity (70).

Recently it has been discussed (71, 72) that disproportional distribution of the mutation of the BRCA2 gene in the geothermal population, compared with the reference populations in the present studies, may be a confounding factor, in particular for the association with breast cancer among women (71, 72). However, this mutation only occurs in 0.6% of the Icelandic population (56) and therefore is not likely to account for our results. Nevertheless, we used the Axelson and Steenland method (53, 54) to quantify the possible influence of this factor on our findings, revealing that although the estimated mutation prevalence is higher in geothermal areas, this increase only account for 3% of the total female breast cancer incidence. Also, BRCA2 mutation carriers have a well-documented increased risk of ovarian cancer (73) and the decreased risk of ovarian cancer in geothermal areas shown in three of the studies, albeit not statistically significant, further argues against confounding effects of mutation in the BRCA2 gene.

The data on reproductive factors, the most important possible confounder in breast cancer studies of this design (52), were available from Statistics Iceland (43). This data suggests that reproductive factors are not positive confounders for breast cancer in these studies. In Iceland, screening mammography has been offered to all women 40 to 69 years of age since 1987, and there are no indications of differences in participation in the screening program according to place of residence.

5.1.3 Prostate cancer

There was an increased risk of prostate cancer in the exposed cohort compared with both reference areas. The known risk factors for prostate cancer are age, area of residence (according to migration studies), ethnic background and family history, and the aetiology is claimed to be extensively studied (74). In the present studies, age is taken into consideration in the calculations and the populations are homogenous Caucasian. Several studies have evaluated nutritional aetiology of prostate cancer; however they have not reached definitive conclusions (74). An Icelandic study found an association between milk intake in early life and risk of advanced prostate cancer (75). This study was confined to a population that had been resident in the capital area at least since 1967; however, the capital area was excluded from the present studies.

5.1.4 Kidney cancer

The incidence of kidney cancer showed a statistically significant increase for both genders combined and among men in comparison with warm and cold reference areas, with and without adjustment for smoking habit. Kidney cancer has been associated with smoking, obesity and hypertension (76). In the present studies, we were only able to control indirectly for smoking.

In a meta-analysis by Saint-Jacques et al. (77), As in drinking water was associated with an increased risk of kidney cancer. In a recent study from Bangladesh it was concluded that the relationship between As concentration in drinking water and renal cancer suggested that As is a causal factor for renal cancer (78).

5.1.5 Non-Hodgkin lymphoma (NHL)

NHL comprises heterogeneous malignancies with regard to their clinical, etiological and histological entity (79). Many infectious agents, immune deficiencies, autoimmunity and high doses of ionizing radiation have been associated with NHL. Furthermore, other possible risk factors are farming, pesticides, hairdressing, textile occupations, organochlorines, red meat and processed meat consumption, besides host factors such as personal and family history of cancer and certain medical conditions (79-82). The association of reproductive factors with NHL is not clear; a Swedish study has shown a protective effect of parity (83), while an Italian study did not support any protection of reproductive factors on the risk of NHL (84). In the present studies, the incidence of NHL was higher when adjusted for age at first birth.

Detailed knowledge of these risk factors among the population of the geothermal areas or the reference areas is not at hand; however considerable agricultural activity and greenhouses were present on some of the areas and lindane has been linked to NHL (85). A previous study on pesticide users in Iceland did not find increased incidence of NHL (86).

A case-control study on Icelandic sheep farmers exposed to lindane showed an increased risk for NHL (87). The distribution of sheep farmers in the population of the present studies is not known, however, most of the sheep farmers have been located outside the capital area.

5.1.6 Myelodysplastic syndromes (MDS)

The HRs for MDS, based on eight cases, were high and the 95% CI did not include unity. The cases of MDS were not secondary to cancer treatment, as the studies are confined to first cancers only, and these cases were not classified as therapy-related, but had the location code D46.9, MDS, unspecified. All cancers in the ICD-10 category D had morphology behavioural code /3 indicating malignant neoplasm. Familial aggregation was not found in patients with MDS in one study (88), and other studies have shown that MDS may arise secondarily after chemotherapy and radiotherapy (89), and exposure to ionizing radiation and benzene increased the risk (90, 91).

5.1.7 Lung cancer

In the study from Rotorua, the association of geothermal gas emissions and cancers of the respiratory system were in focus (33), with some indication of elevated risk for lung cancer. In the studies of this thesis the incidence of lung cancer was not increased and the confidence interval included unity. There is a general agreement on the interaction between Rn exposure and tobacco smoking on one hand and lung cancer risk on the other (38). Breaking down the data on smoking from the Public Health Institute of Iceland (51) into the geographical areas in these studies showed the proportion of never-smokers was fairly equally distributed among the populations studied, although highest in the geothermal areas: 47.6% (based on 479 answers), warm areas: 45.4% (based on 16 187 answers), and cold areas 46.8% (based on 5524 answers). Thus it seems unlikely that smoking habits difference were explaining the findings, as the incidence of lung cancer was not statistically significantly higher in the geothermal area than in the reference areas in the present studies.

5.1.8 Basal cell carcinoma (BCC)

The majority of skin cancers are considered to be attributable to sunlight and ultraviolet radiation (92). Exposure to ultraviolet radiation is not likely to explain the increase in risk of BCC, as no corresponding significant increase in malignant melanoma or other skin cancer is observed in the studies.

Ionizing radiation is a well-known cause of BCC (93, 94) and exposures to Rn and alpha radiation have previously been associated with BCC in a study of uranium miners (95). In that study, surface contamination of the skin by Rn and its progeny was considered of importance, as the basal cell layer of the skin lies within the range of the alpha particles (95). An ecological study in South West England showed an association of residential exposure to Rn and risk of squamous cell carcinoma (96), and a previous study in the same setting also indicated an association of residential exposure to Rn and non-melanoma skin cancers (97). In that study, basal cell carcinoma was included among the non-melanoma skin cancers (97).

5.2 Mortality study (Study III)

This population-based study on nearly a thousand deaths in geothermal areas supplied with geothermal hot water used for heating, bathing and washing for decades, shows increased mortality for breast cancer, prostate cancer, kidney cancer, and non-Hodgkin lymphoma. The increased mortality for breast cancer and prostate cancer in the present study is consistent with the increased incidence of breast cancer among the population in the Furnas village, located in the geothermal area of the volcanic island Sao Miguel, in Azores (9) and increased incidence of breast cancer and prostate cancer in the volcanic region of Catania province in Sicily (36).

Most of the remaining causes of death were in line with averages, and the HRs for diseases of the nervous and circulatory system were close to unity. An exception was an excess for influenza, based on nine cases, but mortality for other diseases of the respiratory system was not increased. In the Rotorua geothermal area study, an increased standardised mortality ratio was found due to all diseases of the respiratory system, confined to female and particularly Maori females, and concerning the subcategories: pneumonia and influenza combined, and chronic obstructive respiratory diseases (98). In the Tuscan geothermal area study, there seemed also to be an excess mortality for all diseases of the respiratory system among males, mainly due to an excess of pneumoconiosis (99). The three- to four-fold increase in mortality for influenza was fairly consistent in comparing the two reference areas and between both genders in the present study. The significance of these findings is uncertain. Mortality for all external causes of death was not significantly increased; however, suicides were increased for both males and females. This was not hypothesised and came unexpectedly, as suicide risk was not mentioned in previous mortality studies from geothermal areas (98, 99) and is here without explanation. In this connection it is worth pointing out that the proportion of individuals living in rural regions was lowest in the geothermal heating area, thus not indicating an overrepresentation of farmers in that population compared with the reference populations. Further, possible social differences were adjusted for, such as education and type of housing, and for estimates of age at first birth (reproductive factor) and smoking habits.

5.3 Geothermal areas and dermal exposure

This thesis highlights the high risk (HR 95% CI) of many cancer sites in geothermal areas compared with cold and warm reference areas. The causes are unknown but are related to duration of cumulative residence in the study areas. It is difficult to explain the risk factor for the different cancer sites by a single component of the ground gas emission, chemical traces in the geothermal areas, or in the geothermal water. As has been mentioned in a recent mortality study on an old volcanic area that provided evidence of association of low dose (below 10 ppb) As in drinking water and cancer risk (100), and in a case-control study, positive association between BCC and a low dose exposure to As was found (101). The concentration of As in geothermal well water used for bathing in the geothermal areas, ranges from 11 to 116 ppb (102), compared with the concentrations of less than 0.3 ppb in the cold reference area (103, 104). According to a recent nation-wide survey of indoor Rn concentration in Iceland, a mean of 13 Bq/m3 is among the lowest in the world (105). Nevertheless, the amount of Rn in the geothermal water (used for bathing) in the geothermal area (9 Bq/l) (17) is approximately four times the amount of Rn in water used for bathing in the cold reference area (approximately 1.5 Bq/l) (18, 103). Recently, NORM has been discovered above exemption limit for the first time in Iceland, located in scale precipitated in pipes close to wells (boreholes) in one of the geothermal power plants (19). The NORM is from the U-238 decay chain and exceeded the exemption limit 10 Bq/g ten to twenty times (19).

The role of these differences in concentrations is unknown. The concentrations of As, Rn and internalized radionuclides, have not been measured for the purpose of the present studies in geothermal areas in comparison with reference areas. Bearing that in mind, dermal exposure may in this situation be of greater importance than exposure through inhalation or ingestion. Water in geothermal areas has been used for bathing and washing, but was not recommended for drinking. However, when the results of these studies were presented in the media in Iceland, some people said that geothermal water in Iceland has indeed been used sometimes for cooking food and making coffee, and even for brushing teeth. At present we do not know whether such use of geothermal hot water is common, or how such habits are distributed among the study populations.

5.4 Further implication

5.4.1 Rate difference

The results of the present studies in this thesis showed high incidence of cancer in geothermal areas compared with to the reference areas, as indicated by the HRs. This raises questions as to how many extra cancer cases have occurred in the geothermal area compared with the warm and cold reference areas, in the 33 years of follow-up (Study IV).

From the figures in Study IV, the rate difference per 100 000 person years was calculated for all cancers combined (50). There were 53 excess cancer cases in the geothermal area compared with the warm reference area and 167 excess cancer cases in geothermal area compared with the cold reference area. The rate difference for BCC was 39 excess cancer cases compared with the warm reference area and 66 excess cancer cases compared with the cold reference area.

5.4.2 Migrations to the capital area

The population living in the capital area (Reykjavik and the southwest peninsula of Reykjanes) have been excluded from the present studies. The reason was that according to the ICR (44), the capital area has had higher cancer incidence than other parts of the country for decades, a well-known phenomenon in cancer registries, sometimes called the capital effect or the metropolitan effect (23, 48, 49).

The intention of this exclusion was to avoid the possibility of confounding by the capital effect, and to increase the comparability of the populations in the present studies.

When crude incidence rates were calculated per 100 000 person years for all cancers combined, in the cold reference area, warm reference area, geothermal area, and capital area, the figures are in agreement with the age-standardized cross-sectional analyses of the ICR (44), that the capital area has the highest incidence of cancer, see Figure 6. The incidence rates for BCC, per 100 000 person years, in the cold reference area, warm reference area, geothermal area and capital area are shown in Figure 7.

For decades, the migration pattern in Iceland is that people have been moving from the areas outside the capital into the capital area (106, 107).

The above-mentioned information indicates that moving to the capital area does not protect from cancer risk.

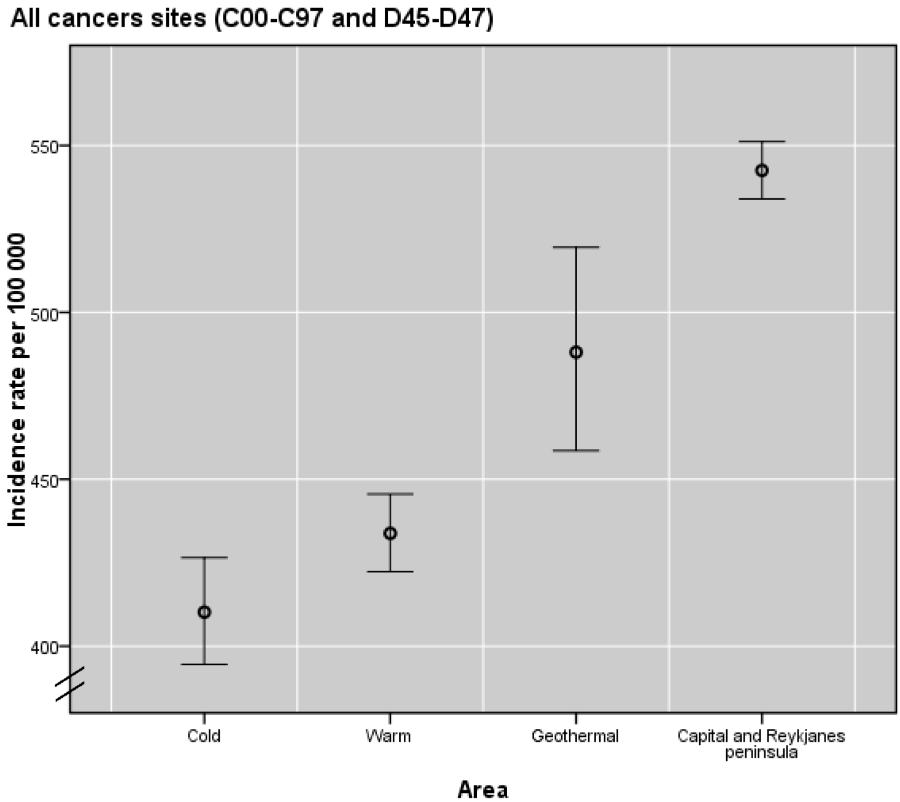

Figure 6 Incidence rates per 100 000 person years, according to all cancers combined in the cold reference area, warm reference area, geothermal area and capital area (Reykjavik and south-west peninsula of Reykjanes).

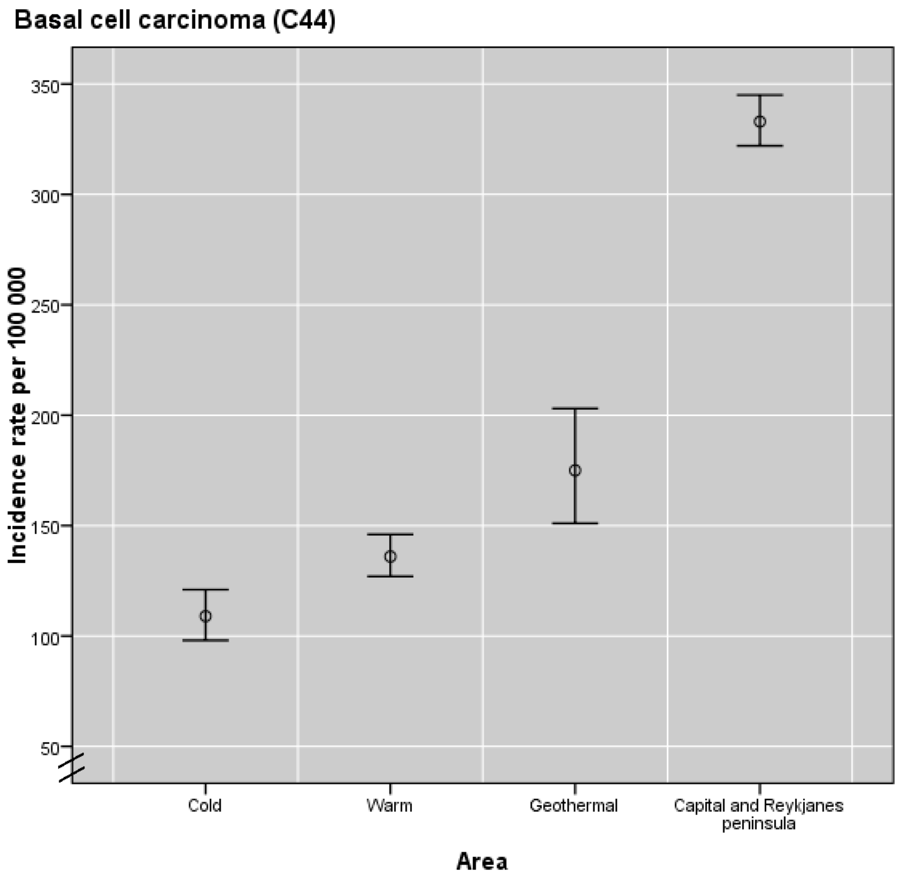

Figure 7 Incidence rates per 100 000 person years, according to BCC in the cold reference area, warm reference area, geothermal area and capital area (Reykjavik and southwest peninsula of Reykjanes).

5.4.3 Detection bias

The possibility of detection bias rises if access to health services across the populations in the present studies is different, and distance from the capital area, where most of the medical specialists and doctors are located per capita, has been used as a gradient of such bias (108). The populations in the present studies are all located outside the capital, but at different distances from the capital area. One may interpret figures 6 and 7 as indicating a detection bias; however, the so-called capital effect has not been explained solely by detection bias (49).

The high mortality for different cancer types in Study III, which was of a similar pattern to the high incidence of cancer in Study IV, do not support the conclusion that the ascertainment of cancer diagnosis was exaggerated in geothermal area. The Study III and IV show that incidence and the mortality of cancers were high in the geothermal area for breast cancer, kidney cancer, prostate cancer and non-Hodgkin lymphoma, compared with the warm and cold reference areas, and 95% CI for these cancers mentioned above did not include unity. Thus it is unlikely that detection bias explains the difference between the cancer rates of the populations in the studies, for these cancer types.

5.5 Strengths and limitations

We count as strength of these studies the long follow-up time of the cohort; to our best knowledge, the follow-up time in our cohort studies is the longest of the populations in geothermal areas to date. Furthermore, the use of the comprehensive population registries and the personal identification number, in accurate record linkage, gave exact identification of the histological confirmed cancer cases from the ICR in the exposed population and in the reference populations.

The duration of residence, vital, and out-migration status (migration from Iceland) was ascertained through the National Rosters, the National Emigration Registry, and the National Cause-of-Death Registry for all individuals in the exposed cohort and the two reference populations, i.e. in the same way for everybody in the studies.

To our best knowledge, the present studies are the first to report the cumulative years of residence for every individual in the geothermal areas (the exposed population) and in the two reference populations, and it enables us to take the length of residence as a surrogate of the exposure to volcanic/geothermal environment, and the use of geothermal water, into consideration in the risk assessments.

Numerous calculations of HRs for all cancers and selected cancer sites were performed in the present studies. The many calculations performed may give rise to concern regarding multiple comparisons; however, it has been argued that no adjustment is needed for these (109).

The studies are limited by the lack of individual exposure information with regard to mode and magnitude of ground gas emission in the geothermal area and the reference areas, and the detailed information on the components of the drinking water and the geothermal water, which may be of importance in the studies. However, we were able to take length of residence in the areas into consideration as a surrogate of exposure. The possibility of unknown confounding cannot be excluded; however in the multivariate analysis, we were able to adjust for socioeconomic status (level of education, and type of housing), age, and gender on an individual level, and smoking habits and age at first birth on a community level. It has been shown that access to the health care system was found to be easier and the use of the health care system was found to be more frequent, concerning cardiovascular diseases, outside than inside the capital area in Iceland (108). However, we are not aware of differences in these aspects between the study populations.

Over time, geothermal water has become more widely used in Iceland which is making it difficult to identify populations without exposure. One way to address this problem in future studies is to select the reference population from communities without use of the geothermal water, in order to avoid possible confounding regarding this.

5.6 Future studies

The chemical and physical content of the environmental emissions in geothermal areas, and the dermal contamination resulting from the use of geothermal water will be main challenges in future studies.

Questionnaire studies on the possible use of the geothermal hot water as drinking water are essential. The hygienic control of drinking water in Iceland has foremost aimed at the cold drinking water supply and not the geothermal water, and it may be that the public health authorities have assumed that it was not necessary to control the geothermal water, based on the assumption that it is not used as drinking water.

The comprehensive Icelandic population registries offer a unique opportunity for further studies of these issues. Possible studies may concentrate on cancer risk according to continuous time of residence in the study areas as well as time of residence and migrations between study areas and other regions in Iceland. Possible studies include the risk of second cancer and third cancer, and risk of cancer according to access to health service across regions in Iceland and distance from the capital area. Internal analyses of the risk of different cancer types among the populations of the exposed and unexposed areas would also be of interest. Several case-control studies are possible on the etiology of cancers of breast, pancreas, lung, prostate, kidney, lymphoid and haematopoietic tissue, NHL, BCC of the skin and other skin cancers. Extended follow-up of the mortality study is one idea. For studies on the association of cancer with building materials, the age of houses, maintenance/condition of houses, and the mode of heating houses, information on these factors may be at hand in the census.

The suggestions of possible studies mentioned above are not exhaustive and the Icelandic census data provides an exceptional opportunity to gain knowledge. The result of future studies could be used in prevention of cancer occurrence.

6 Conclusions

The result of the studies indicates higher cancer risk in geothermal areas. Many cancer sites had high incidence and statistically significant higher risk was found for all cancers combined, breast cancer, pancreas cancer, prostate cancer, kidney cancer, combined cancers of the lymphoid and haematopoietic tissue, NHL, and BCC of the skin in the population of the geothermal area compared with the reference areas. The significant excess mortality risk was also found in breast cancer and prostate cancers, kidney cancer, and NHL, and the cancer risk is thus not confined to cancers with good prognosis, but also concerns fatal cancers.

Positive dose-response manner of the relationship between incidence of cancers and cumulative years of residence, and gradient of geothermal/volcanic activity were shown. Applying a five-year latency time yielded higher cancer risk. Adjustment was made for individual social-related variables, as well as for reproductive factors and smoking habits on the community level.

Further studies are needed on the chemical and physical content of the environmental emissions in geothermal areas, and the role of dermal contamination resulting from the use of geothermal water, and possible other exposure to geothermal water, in an attempt to identify known and/or unknown carcinogenic agents.

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Paper I

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ENVIRONMENTAL HEALTH

RESEARCH Open Access

Incidence of cancer among residents of high temperature geothermal areas in Iceland: a census based study 1981 to 2010

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Abstract

Background: Residents of geothermal areas are exposed to geothermal emissions and water containing hydrogen sulphide and radon. We aim to study the association of the residence in high temperature geothermal area with the risk of cancer.

Methods: This is an observational cohort study where the population of a high-temperature geothermal area (35,707 person years) was compared with the population of a cold, non-geothermal area (571,509 person years). The cohort originates from the 1981 National Census. The follow up from 1981 to 2010 was based on record linkage by personal identifier with nation-wide death and cancer registries. Through the registries it was possible to ascertain emigration and vital status and to identify the cancer cases, 95% of which had histological verification. The hazard ratio (HR) and 95% confidence intervals (CI) were estimated in Cox-model, adjusted for age, gender, education and housing.

Results: Adjusted HR in the high-temperature geothermal area for all cancers was 1.22 (95% CI 1.05 to 1.42) as compared with the cold area. The HR for pancreatic cancer was 2.85 (95% CI 1.39 to 5.86), breast cancer 1.59 (95% CI 1.10 to 2.31), lymphoid and hematopoietic cancer 1.64 (95% CI 1.00 to 2.66), and non-Hodgkin´s lymphoma 3.25 (95% CI 1.73 to 6.07). The HR for basal cell carcinoma of the skin was 1.61 (95% CI 1.10 to 2.35). The HRs were increased for cancers of the nasal cavities, larynx, lung, prostate, thyroid gland and for soft tissue sarcoma; however the 95% CIs included unity.

Conclusions: More precise information on chemical and physical exposures are needed to draw firm conclusions from the findings. The significant excess risk of breast cancer, and basal cell carcinoma of the skin, and the suggested excess risk of other radiation-sensitive cancers, calls for measurement of the content of the gas emissions and the hot water, which have been of concern in previous studies in volcanic areas. There are indications of an exposure-response relationship, as the risk was higher in comparison with the cold than with the warm reference area. Social status has been taken into account and data on reproductive factors and smoking habits show that these do not seem to explain the increased risk of cancers, however unknown confounding can not be excluded.

Keywords: Breast cancer, Basal cell carcinoma of skin, Pancreatic cancer, Non-Hodgkin's lymphoma, Radon

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Background

Through the centuries, volcanic eruptions in Iceland have now and then emitted ash and gases, which have been carried downwind to mainland Europe; and historically such events have been associated with climate change and increased mortality in England and elsewhere [1]. Recent volcanic activities in Iceland have disturbed commercial air traffic for weeks in the years 2010 and 2011 [2,3]. People living in the close vicinity of the volcano are usually those who suffer most in cases of eruption [4]. Fortunately the eruptions do not usually last for months, although it does happen. However people living on volcanic ground may experience long-term exposure to various toxic ground gas emissions, carbon dioxide (CO_2), hydrogen sulphide (H_2S), radon (Rn), sulphur dioxide (SO_2), sulphuric acid (H_2SO_4), hydrogen chloride (HCl), and hydrogen fluoride (HF), and these are considered to pose chronic health hazards [5-7]. Several other low-dose exposures have been mentioned, among them arsenic (As), lead (Pb), and mercury (Hg) [8]. The risk of cancer among these populations has so far been the subject of only limited study and the results have been inconsistent [8-10]. In the study from Rotorua, New Zealand, Bates et al. suggested an association of nasal and lung cancer with residence in a geothermal field, and particularly exposure to H_2S, [9] although exposure to Rn was not high, according to later estimates [7] The study from the Azores, Portugal, found an association of female breast cancer with residence on an actively degassing geothermal field, and in that study, Amaral et al. suggested that trace elements and high Rn exposure might play a role [8]. In a study from Sicily, residents of the volcanic region of Catania province seem to have higher incidence of thyroid cancer than other populations and it is mentioned that the concentration of Rn is elevated in the environment in the area [10]. However, the authors were not able to conclude on the association of Rn exposure with the risk of thyroid cancer [10].

Geothermal water and steam have been used for decades in Iceland for domestic heating, bathing and showering, and in various industries [11,12]. In the year 2000, when seismological studies were conducted, the concentration of Rn measured 1.3 Bq/l to 9 Bq/l [13] in geothermal hot water from drilled wells. Radon gas and its progeny are the major contributors to radiation exposure of the general population and are classified as carcinogenic by the International Agency for Research of Cancer (IARC), based on an increase in lung cancer among exposed human populations [14].

The aim was to study whether residence in a high-temperature geothermal area, where inhabitants are exposed to geothermal emissions and water containing hydrogen sulphide and radon, is associated with the risk of cancer.

Methods

Geologically, Iceland is a young island located in the North Atlantic Ocean on the boundary between the North American and Eurasian tectonic plates. These two plates are moving apart at a rate of about 2 cm per year and Iceland is an anomalous part of the ridge where deep mantle material wells up and creates a hot spot of unusually great volcanic productivity and several geothermal fields [11,12]. Iceland has a homogenous Caucasian population that grew from 229,000 in 1981 to 318,000 in 2010, the period that the study spanned [15].

This is a population-based observational study. The source of data for the cohort was the 1981 National Census in Iceland, kept at Statistics Iceland. In the census, each individual is filed under a personal identification number that is allocated to individuals at birth. The census included information on gender, age, residency, education, and the type of residence. The cohort for this study was confined to people aged 5 to 65 years at the time of the census. The personal identification numbers were used in record linkage with the National Registry to obtain information, where applicable, on the date of emigration and with the National Cause-of-Death Registry to obtain information on vital status and, where applicable, the date of death. Both these registries are kept at Statistics Iceland. In this way, it was possible to ascertain the vital and emigration status for the entire cohort. Thus it was possible to define person years at risk for each individual. Those who emigrated could not be followed up in the cancer registry after the date of emigration, even in cases where they subsequently returned.

The Icelandic Cancer Registry, established in 1955, is a nation-wide registry of all cases of cancer. The registry has virtually complete coverage and over 95% of the diagnoses are histologically confirmed [16]. The topography codes used during the study period were according to ICD-7, ICD-9, and ICD-10; however they were standardized by the registry to ICD-10, and the morphology was registered according to ICD-03. Basal cell carcinoma (BCC) has been registered since 1981 in a special file at the cancer registry. It is not counted with the overall cancers and these cases are analysed separately. The computer file of individuals in the census was linked to the Icelandic Cancer Registry by their personal identification numbers. Thus, we were able to establish whether these individuals had cancer, and if so, to identify the cancer site, morphology, and date of diagnosis.

The four-digit community code in the census was used to identify the populations living in two communities located in high-temperature geothermal areas. The first of these communities is a small town in southern

Iceland (Hveragerdi), where geothermal hot water has been used since 1950 for heating greenhouses and for domestical heating, laundry, bathing, showering, and washing dishes. Geothermal hot water in Iceland is not used as drinking water, as it is unpalatable and foul smelling because of the gas and mineral content, and there is an abundance of other water sources available. The area surrounding Hveragerdi forms part of the Hengill central volcano and there are many hot springs, fumaroles and erupting geysers in the town. The second community is smaller and consists of a small town and agricultural district (Skutustadahreppur, Myvatn), located in the north-eastern part of Iceland, where geothermal hot water has been used since 1967 in industry and for domestic heating, laundry, bathing, showering, and washing dishes. This community is on the edge of the Krafla volcano. Fumes from geothermal activities are frequently seen in these communities and the rotten egg odour of hydrogen sulphide is often perceived. Both these communities are inland regions, unlike most communities in Iceland that are located in coastal regions. The geothermal field in these communities belongs to the high-temperature geothermal areas where the underground temperature at 1,000 m depth is above 150°C, and the bedrock is less than 0.8 million years old, according to descriptions of the volcanic and geothermal zones in Iceland [11,12].

The two comparison populations, classified according to the community codes in the census, included residents of communities other than these high-temperature geothermal areas. The first of these comparison populations included residents living well outside of the volcanic zone, in what we call the cold reference area, where the bedrock is more than 3.3 million years old and the underground temperature at 1,000 m depth is below 150°C [11,12]. The population of the cold reference area is considered the main comparison population in the study. The second comparison population included those living within the volcanic zone, where the bedrock dates from different periods, [11,12] referred to here as the warm reference area. The people in the warm reference area may or may not be living in the vicinity of geothermal fields, as these are spread out over the whole country. However, the community codes did not allow for differentiation between those exposed to high-temperature geothermal fields and those who are not, so this population is considered to have a mixed exposure. The rest of population living in the capital Reykjavik and in the south-west peninsula of Reykjanes were excluded from the study. The reason were that according to the cancer registry, the capital and south-west area has had higher cancer incidence than other parts of the country for decades [16]. The geology and the location of the areas are shown in Figures 1 and 2.

The follow up started at the day of the census, 31 January 1981, and concluded at the date of emigration, or of death, or the date of diagnosis of cancer, or 31 December 2010 (the end of the follow up period), whichever occurred first. The dependent variables for this study were the incidence of first cancer occurring 31 January 1981 to 31 December 2010. The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI) for all cancers and selected cancer sites in time-dependent analyses [17]. Gender was introduced as a dichotomous variable, and age as a continuous variable in years. Educational level (basic, medium and academic education), was introduced as a categorical variable according to the previous classification in a census study [18] with an additional two categories: one, unclassified for people under 20 years of age, who had not yet attained their full education level, and one missing educational information for individuals who did not indicate their education in the census. Type of residence, single-family house or other type of residence, was introduced as a dichotomous variable. According to Statistics Iceland, we divided the whole population into those living in the capital region, other urban regions and rural regions [15]. The exposed population living in the high-temperature geothermal areas was compared with the other two populations (warm reference area and cold reference area) in separate analyses. We did several calculations in the model: crude comparison without any adjustments, comparison with adjustment for age and gender only, and with adjustment for age, gender, educational level, and lodging. These three models, as well as the calculations done by introducing age stratified in 10-year age groups, had nearly identical results. Only the results with all the adjustments are presented here. All cancer sites with any cancer case are shown in the tables for completeness, and sites with no case are not shown. In cases where there were few instances of the cancer site, the confidence intervals were computed by a bootstrap resampling method. Separate analyses were done after dividing the material into gender and groups of individuals who were 20 years of age or older at the time of the census and those who were under 20 years of age, in order to investigate possible bias from childhood cancer. The statistical analyses were performed using the PASW (SPSS) software version 18, STATA, and Microsoft Excel 2007.

The National Bioethics Committee (VSNb2010060005/03.1) and the Data Protection Commission (2010060524ÞPJ/–) approved the study.

Results

The number of individuals aged 5 to 65 years included in the census was 184,114, and the number of persons in

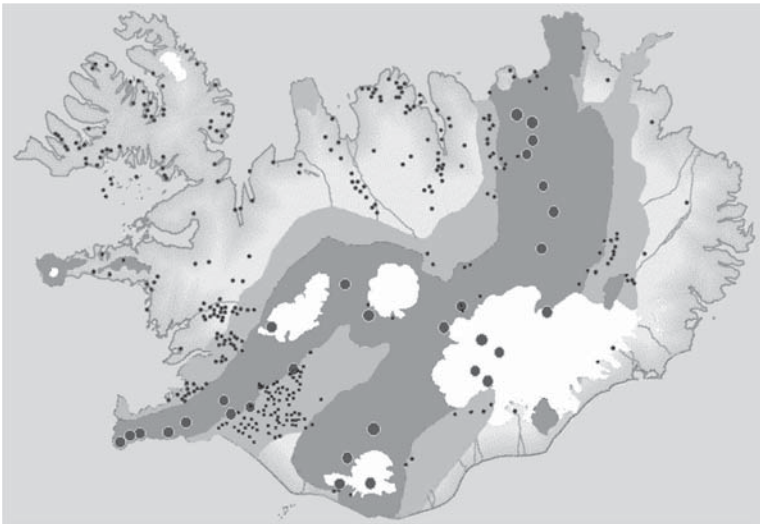

Figure 1 Geological map of Iceland, showing the distribution of natural geothermal activity and the age of bedrock. Modified with permission from National Energy Authority. Small circles low temperature geothermal field, large circles high temperature geothermal field, age of bedrock: < 0.8, to gray 0.8-3.3, to light gray 3.3-15, and white glaciers.

the same age range in the National Registry was 185,610 at the time of the census, thus 99.2% were included in the census.

The number of individuals in the study was 74,806 and altogether there were 1901,786 person-years in the study. The average follow-up was 24.9 years. A total of 7,689 (4,039 men and 3,650 women) cases of first cancer were identified through the cancer registry, and there were 1,028 cases of first BCC (463 men and 565 women). During the follow up 10,570 individuals (5,599 men and 4,971 women) had emigrated and 6,458 (4,040 men and 2,418 women) had died. At the end of the study on 31 December 2010 there were 50,089 (25,449 men and 24,640 women) individuals alive without cancer.

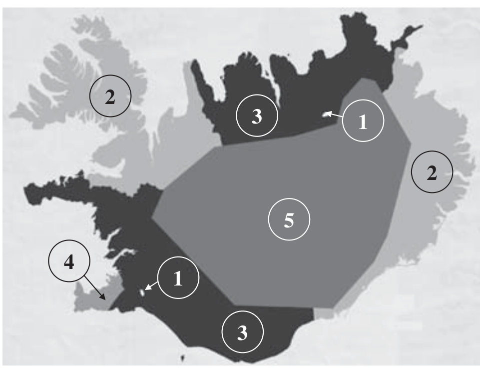

Figure 2 Map of Iceland, showing the study areas according to the community codes: 1) High-temperature geothermal area. 2) Cold reference area. 3) Warm reference area. 4) Capital and South West area. 5) Uninhabited area. Modified with permission from National Land Survey of Iceland.

Table 1 shows the characteristics of the cohort according to the 1981 census. The proportion of men was 52% and of women, 48%. The high-temperature geothermal areas were exclusively rural regions, the cold reference area was a mixture of other urban and rural regions, and the warm reference area was 40% other urban and 60% rural regions. As these variables have extreme and different distribution among the areas, it was not possible to enter them into the Cox-model; however, the cold area resembles the high-temperature geothermal areas with regard to these variables.

Table 2 shows the number of all cancers, and selected cancer sites in the high-temperature geothermal areas, and the HR and 95% CI. During the follow up, 184 cases of cancers were diagnosed among men and women in the high-temperature geothermal areas and the HRs for all sites were 1.16 (95% CI 1.00 to 1.34) and 1.22 (95% CI 1.05 to 1.42) compared with the warm reference area and the cold reference area respectively. The HRs for pancreatic cancer were 2.57 (95% CI 1.30 to 5.07), and 2.85 (95% CI 1.39 to 5.86) compared with the warm reference area and the cold reference area respectively. The HRs for bone cancer were 3.56 (95% CI 0.83 to

Table 1 Baseline characteristics in the high-temperature geothermal areas and different reference areas according to census 1981

	Geothermal areas N (%)	Warm reference area N (%)	Cold reference area N (%)
Number of people	1,497 (100)	50,878 (100)	22,431 (100)
Gender			
Men	767 (51.2)	26,431 (51.9)	11,929 (53.2)
Woman	730 (48.8)	24,447 (48.1)	10,502 (46.8)
Age, year			
Mean ± SD	29.69 ± 17.22	28.12 ± 16.28	28.06 ± 16.20
Median, IQR (0.25 ; 0.75)	27 (15 ; 43)	25 (15 ; 40)	25 (15 ; 39)
Education			
Basic education	368 (24.6)	13,831 (27.2)	6,565 (29.3)
Medium education	428 (28.6)	13,414 (26.4)	5,665 (25.3)
Academic education	140 (9.4)	3,653 (7.2)	1,428 (6.4)
Unclassified	535 (35.7)	19,404 (38.1)	8,481 (37.7)
Missing	36 (1.7)	576 (1.1)	292 (1.3)
Housing			
Single family home	1,205 (80.5)	33,761 (66.4)	17,343 (77.3)
Other type of house	292 (19.5)	17,117 (33.6)	5,088 (22.7)
Region			
Capital region	0	0	0
Other urban regions	0	20,958 (41.2)	4,863 (21.7)
Rural regions	1,497 (100.0)	29,920 (58.8)	17,568 (78.3)

Abbreviations: *SD* standard deviation, *IQR* interquartile range.

15.27), and 5.80 (95% CI 1.11 to 30.32) compared with the warm reference area and the cold reference area respectively, based on two cases; however, the CIs according to the bootstrap method were wide and included unity. The HRs for breast cancer were 1.43 (95% CI 1.00 to 2.05), and 1.59 (95% CI 1.10 to 2.31) compared with the warm reference area and the cold reference area respectively. The HRs for all cancers of lymphoid and haematopoietic tissue combined were 1.53 (95% CI 0.95 to 2.46), and 1.64 (95% CI 1.00 to 2.66) compared with the warm reference area and the cold reference area respectively. The HRs for non-Hodgkin´s lymphoma (NHL) were 3.21 (95% CI 1.77 to 5.82), and 3.25 (95% CI 1.73 to 6.07) compared with the warm reference area and the cold reference area respectively. The HRs for several other cancer sites were increased, but these were based on few cases and with wide confidence intervals. The HRs for the 30 cases of BCC in the high-temperature geothermal areas were 1.37 (95% CI 0.95 to 1.97), and 1.61 (95% CI 1.10 to 2.35) compared with the warm reference area and the cold reference area respectively, shown in the lowest row of Table 2.

Among men, 90 cases of cancer were in the high-temperature geothermal areas. Table 3 shows the number of all cancers and selected cancer sites, and the HR and 95% CI. The HRs for pancreatic cancer were 2.52 (95% CI 1.01 to 6.28), and 3.66 (95% CI 1.37 to 9.82) compared with the warm reference area and the cold reference area respectively. The HRs for NHL were 3.12 (95% CI 1.43 to 6.78), and 2.58 (95% CI 1.16 to 5.78) compared with the warm reference area and the cold reference area respectively. The HRs for the 15 cases of BCC were 1.52 (95% CI 0.90 to 2.55), and 1.78 (95% CI 1.04 to 3.05) compared with the warm reference area and the cold reference area respectively.

Among women, 94 cases of cancer were in the high-temperature geothermal areas and Table 4 shows the number of all cancers and selected cancer sites, and the HR and 95% CI. The HRs for all sites were 1.27 (95% CI 1.03 to 1.56), and 1.30 (95% CI 1.05 to 1.61) compared with the warm reference area and the cold reference area respectively. The HRs for bone cancers were 7.95 and 7.20 compared with the warm reference area and the cold reference area respectively, based on two cases; however the CIs according to the bootstrap method were wide and included unity. The HRs for breast cancer were 1.46 (95% CI 1.02 to 2.09), and 1.62 (95% CI 1.12 to 2.36) compared with the warm reference area and the

Table 2 Number of all cancers and selected cancer sites among men and women combined in the high-temperature geothermal areas, hazard ratio (HR), 95% confidence intervals (CI) according to compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, and type of housing

Cancers (ICD-10)	Geothermal areas	Warm reference area		Cold reference area	
	p-yr 35,707	p-yr 1294,570		p-yr 571,509	
	No of cancers	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	184	**1.16**	**1.00 to 1.34**	**1.22**	**1.05 to 1.42**
Lip, oral cavity, and pharynx (C00-C14)	2	0.64	0.16 to 2.60	0.81	0.20 to 3.38
Oesophagus (C15)	1	0.50	0.07 to 3.58	0.58	0.08 to 4.20
Stomach (C16)	7	1.13	0.53 to 2.41	0.99	0.46 to 2.14
Colon, rectum, and anus (C18-C21)	16	1.13	0.69 to 1.86	1.17	0.70 to 1.94
Bile and liver (C22-C24)	2	0.95	0.23 to 3.88	1.02	0.24 to 4.29
Pancreas (C25)	9	**2.57**	**1.30 to 5.07**	**2.85**	**1.39 to 5.86**
Nasal cavity and middle ear (C30)	1	3.32	0.42 to 26.32	2.58	0.30 to 22.33
Larynx (C32)	2	2.21	0.53 to 9.30	3.04	0.66 to 13.98
Lung and bronchus (C33-C34)	20	1.24	0.80 to 1.95	1.11	0.70 to 1.75
Bone (C40-C41)	2	3.56	0.83 to 15.27*	**5.80**	**1.11 to 30.32***
Melanoma (C43)	2	0.51	0.13 to 2.04	0.62	0.15 to 2.56
Other cancer of skin (C44)	4	0.84	0.31 to 2.27	1.01	0.37 to 2.79
Soft tissue sarcoma (C49)	2	1.86	0.45 to 7.78	1.97	0.45 to 8.66
Breast (C50)	31	**1.43**	**1.00 to 2.05**	**1.59**	**1.10 to 2.31**
Vulva (C51)	1	4.03	0.50 to 32.36	2.96	0.34 to 25.58
Cervix uteri (C53)	2	0.85	0.21 to 3.45	1.04	0.25 to 4.37
Uterus (C54-C55)	3	0.82	0.26 to 2.60	0.88	0.27 to 2.82
Ovary (C56-C57)	5	1.25	0.51 to 3.05	1.25	0.50 to 3.12
Prostate (C61)	29	1.16	0.80 to 1.68	1.37	0.93 to 2.00
Kidney (C64-C66)	5	0.67	0.28 to 1.62	0.83	0.34 to 2.04
Bladder (C67)	8	1.12	0.56 to 2.28	1.02	0.50 to 2.10
Brain and central nervous system (C70-C72, C75.1 and C75.3)	5	0.82	0.34 to 2.00	0.90	0.37 to 2.23
Thyroid gland (C73)	6	1.51	0.66 to 3.42	1.51	0.65 to 3.50
Cancer without specification of site (C80)	1	0.32	0.04 to 2.26	0.28	0.04 to 2.05
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	18	1.53	0.95 to 2.46	**1.64**	**1.00 to 2.66**
Hodgkin´s lymphoma (C81)	1	1.03	0.14 to 7.56	1.50	0.19 to 11.61
Non-Hodgkin´s lymphoma (C82-C85)	12	**3.21**	**1.77 to 5.82**	**3.25**	**1.73 to 6.07**
Immunoproliferative diseases (C88)	1	1.31	0.18 to 9.76	2.00	0.24 to 16.40
Leukaemia (C91-C95 and D45-D47)	4	1.07	0.39 to 2.89	1.07	0.39 to 2.95
Chronic lymphocytic leukaemia (CLL)(C91.1)	1	0.76	0.10 to 5.54	0.70	0.09 to 5.24
Non-CLL (C91-C95 and D45-D47, except C91.1)	3	1.23	0.39 to 3.90	1.30	0.40 to 4.22
Not included in all cancers	p-yr 36,606	p-yr 1320,220		p-yr 581,772	
Basal cell carcinoma of the skin	30	1.37	0.95 to 1.97	**1.61**	**1.10 to 2.35**

Abbreviation: *p-yr*, person years.
Statistically significant HRs are bolded.
* 95% *CI* computed with bootstrap method were wide and included unity.

cold reference area respectively. The HRs for NHL were 3.31 (95% CI 1.32 to 8.34), and 5.20 (95% CI 1.87 to 14.45) compared with the warm reference area and the cold reference area respectively.

When confined to individuals 20 years of age and older and excluding those with missing information on education in the 1981 census, there were altogether 172 cancer cases in the high-temperature

Table 3 Number of all cancers and selected cancer sites among men only in the high - temperature geothermal areas, hazard ratio (HR), 95% confidence intervals (CI) according to comparison with the populations in warm reference area and cold reference area, adjusted for age, gender, education, and type of housing

Cancers (ICD-10)	Geothermal areas	Warm reference area		Cold reference area	
	p-yr 18,181	p-yr 667,069		p-yr 300,297	
	No of cancer	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	90	1.06	0.86 to 1.30	1.14	0.92 to 1.42
Lip, oral cavity, and pharynx (C00-C14)	2	0.99	0.24 to 4.03	1.14	0.27 to 4.82
Oesophagus (C15)	1	0.63	0.09 to 4.55	0.91	0.12 to 6.86
Stomach (C16)	4	1.02	0.38 to 2.77	0.78	0.29 to 2.14
Colon, rectum, and anus (C18-C21)	9	1.12	0.58 to 2.18	1.14	0.58 to 2.25
Bile and liver (C22-C24)	1	0.68	0.09 to 4.93	1.37	0.17 to 10.83
Pancreas (C25)	5	**2.52**	**1.01 to 6.28**	**3.66**	**1.37 to 9.82**
Nasal cavity and middle ear (C30)	1	6.46	0.75 to 55.75	13.08	0.79 to 215.51
Larynx (C32)	2	2.78	0.65 to 11.81	4.30	0.89 to 20.84
Lung and bronchus (C33-C34)	9	1.00	0.52 to 1.94	0.95	0.48 to 1.86
Other cancer of skin (C44)	3	1.12	0.35 to 3.54	1.22	0.38 to 3.98
Soft tissue sarcoma (C49)	1	1.62	0.22 to 12.13	2.52	0.30 to 21.04
Prostate (C61)	29	1.16	0.80 to 1.68	1.37	0.93 to 2.00
Kidney (C64-C66)	2	0.43	0.11 to 1.74	0.54	0.13 to 2.22
Bladder (C67)	7	1.24	0.58 to 2.65	1.11	0.52 to 2.41
Brain and central nervous system (C70-C72, C75.1 and C75.3)	2	0.65	0.16 to 2.64	0.70	0.17 to 2.89
Thyroid gland (C73)	1	0.73	0.10 to 5.30	1.08	0.14 to 8.21
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	11	1.59	0.87 to 2.91	1.62	0.87 to 3.02
Non-Hodgkin´s lymphoma (C82-C85)	7	**3.12**	**1.43 to 6.78**	**2.58**	**1.16 to 5.78**
Leukaemia (C91-C95 and D45-D47)	4	1.73	0.63 to 4.75	1.68	0.60 to 4.74
Chronic lymphocytic leukaemia (CLL)(C91.1)	1	1.33	0.18 to 9.84	1.19	0.16 to 9.14
Non-CLL (C91-C95 and D45-D47, except C91.1)	3	1.95	0.61 to 6.25	2.00	0.60 to 6.66
Not included in all cancers	p-yr 18,463	p-yr 678,577		p-yr 305,053	
Basal cell carcinoma of the skin	15	1.52	0.90 to 2.55	**1.78**	**1.04 to 3.05**

Abbreviation: *p-yr*, person years.
Statistically significant HRs are bolded.

geothermal areas. In this older part of the cohort, the comparison of the high-temperature areas with the cold reference area yielded similar HRs as in the total exposed cohort. The HRs were somewhat lower and the 95% confidence intervals were a little wider, but the intervals were still not including unity for all cancers, pancreatic cancer, breast cancer and NHL. The HR for BCC was 1.52 (95% CI 1.01 to 2.73) based on 26 cases.

In the analysis of those who were under 20 years of age at the census, there were 12 cancers, three among men and nine among women, in the high-temperature geothermal areas. The mean age in this group of cancer cases was 16 years (range 11 to 19 years) at the 1981 census, and the mean age at diagnosis of the cancer was 33.4 years (range 18 to 45 years). The HR for breast cancer was 2.99 (95% CI 1.03 to 8.66), based on four cases, when comparing this younger part of the exposed cohort with the cold reference area. For other cancer sites there were fewer cases. The HR for BCC was 2.70 (95% CI 0.94 to 7.73) based on four cases.

Discussion

This study based on 184 cancer cases in high-temperature geothermal areas showed an excess for all cancers as compared with the reference areas. There is evidence of an exposure-response relationship, as the HRs were higher in the comparison with the cold reference area than with the warm reference area. The most significant results are the excess of BCC in the total cohort based on 30 cases, and the excess of breast cancer and NHL among women and the excess of NHL and pancreatic cancer among men. Many of these cancer

Table 4 Number of all cancers and selected cancer sites among women only in the high - temperature geothermal areas, hazard ratio (HR), 95% confidence intervals (CI) according to comparison with the populations in warm reference area and cold reference area, adjusted for age, gender, education, and type of housing

Cancers (ICD-10)	Geothermal areas	Warm reference area		Cold reference area	
	p-yr 17,526	p-yr 627,500		p-yr 271,213	
	No of cancer	HR	95%CI	HR	95%CI
All sites (C00-C97 and D45-D47)	94	**1.27**	**1.03 to 1.56**	**1.30**	**1.05 to 1.61**
Stomach (C16)	3	1.33	0.42 to 4.22	1.55	0.46 to 5.14
Colon, rectum and anus (C18-C21)	7	1.16	0.54 to 2.46	1.24	0.57 to 2.70
Bile and liver (C22-C24)	1	1.54	0.21 to 11.56	0.82	0.11 to 6.17
Pancreas (C25)	4	2.68	0.96 to 7.45	2.26	0.78 to 6.52
Lung and bronchus (C33-C34)	11	1.56	0.85 to 2.86	1.26	0.68 to 2.33
Bone (C40-C41)	2	**7.95**	**1.70 to 37.23***	**7.20**	**1.30 to 39.96***
Melanoma (C43)	2	0.85	0.21 to 3.46	0.85	0.20 to 3.53
Other cancer of skin (C44)	1	0.48	0.07 to 3.43	0.66	0.09 to 4.91
Soft tissue sarcoma (C49)	1	2.21	0.29 to 16.90	1.62	0.20 to 12.90
Breast (C50)	31	**1.46**	**1.02 to 2.09**	**1.62**	**1.12 to 2.36**
Vulva (C51)	1	4.03	0.50 to 32.36	2.96	0.34 to 25.58
Cervix uteri (C53)	2	0.85	0.21 to 3.45	1.04	0.25 to 4.37
Uterus (C54-C55)	3	0.82	0.26 to 2.60	0.88	0.27 to 2.82
Ovary (C56-C57)	5	1.25	0.51 to 3.05	1.25	0.50 to 3.12
Kidney (C64-C66)	3	1.04	0.33 to 3.29	1.27	0.39 to 4.16
Bladder (C67)	1	0.67	0.09 to 4.85	0.65	0.09 to 4.85
Brain and central nervous system (C70-C72, C75.1 and C75.3)	3	1.01	0.32 to 3.20	1.11	0.34 to 3.62
Thyroid gland (C73)	5	1.92	0.78 to 4.74	1.65	0.65 to 4.18
Cancer without specification of site (C80)	1	0.55	0.08 to 4.01	0.56	0.08 to 4.11
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	7	1.46	0.68 to 3.12	1.66	0.76 to 3.63
Hodgkin´s lymphoma (C81)	1	2.13	0.28 to 16.22	4.42	0.49 to 39.63
Non-Hodgkin´s lymphoma (C82-C85)	5	**3.31**	**1.32 to 8.34**	**5.20**	**1.87 to 14.45**
Immunoproliferative diseases (C88)	1	4.38	0.54 to 35.34	11.92	0.72 to 197.59
Not included in all cancers	p-yr 18,143	p-yr 641,643		p-yr 276,719	
Basal cell carcinoma of the skin	15	1.24	0.74 to 2.08	1.45	0.85 to 2.47

Abbreviation: *p-yr*, person years.
* 95% CI computed with bootstrap method were wide and included unity.
Statistically significant HRs are bolded.

sites, which in the present study are found increased were not included in previous studies of the populations of geothermal areas [8-10]. However, breast cancer was found in excess among the female population of Furnas, Azores [8] and in that study a high rate for cancer of the lip, oral cavity and pharynx was found, although it was based on few cases.

Pancreatic cancer

There was a high rate of pancreatic cancer in the total exposed cohort and among men and a non-significant elevated rate among women; male gender is one of the risk factors for pancreatic cancer. The most important external risk factor for this malignancy, smoking, is not known on an individual basis, but information on smoking in these populations is accessible from the annual surveys of the Public Health Institute of Iceland [19] from the year 1989 to 2010. These data show that the number of smokers has been declining from 31.0% to 14.2% in the population over the period, and the number of smokers has been similar in the capital area and in the rest of the country for decades, so smoking habits are not likely to be a confounder. Supporting this view is the fact that the lung cancer rate was not statistically increased in the exposed cohort. There is no obvious connection of the geothermal field pollution and pancreatic cancer, as the carcinogenic effect of Rn has in most of the studies been related to lung cancer. However, in a collaborative analysis of 11 studies of Rn-exposed underground miners, Darby et al. found an O/E of 1.05, 95% CI 0.85 to 1.29, for pancreas cancer mortality, and that mortality for pancreatic cancer was significantly related to cumulative exposure [20]. In the conclusion of that study, this relation was dismissed, despite the fact that pancreatic cancer is with high mortality and therefore suitable for a mortality study, as compared to cancers with better prognosis. The Rn exposure of miners is higher than Rn exposure in studies on residents.

Breast cancer

As indicated previously, the elevated incidence of breast cancer is in line with the finding in the much smaller study on the population in Furnas, [8] and the authors concluded that the increased risk of breast cancer may be partially explained by the gas emission, trace elements and Rn exposure. Besides the Portuguese study [8] there is scanty literature on the association of exposure to Rn and cancer among women: there were no female workers in the mining populations [21] and the case–control studies on residential exposure to Rn did not deal with breast cancer.

Data on reproductive factors, the most important possible confounder in breast cancer studies of this design, [22] were available from Statistics Iceland [15]. Between 1991 and 1995, the fertility rate for the high-temperature geothermal areas was 2.2, for the warm reference area 2.2, and for the cold reference area 2.3. The figures for mean age at first birth were 22.6 for the high-temperature geothermal areas, 23.1 for the warm reference area, and 23.3 for the cold reference area. This information suggests that reproductive factors are not positive confounders for breast cancer in this study.

In Iceland screening with mammography have been offered to all women 40 to 69 years of age since 1987, and there are no indications of differences in participation in the screening program according to residency.

Bone cancer

The best known etiological factors for bone cancer are ionizing radiation, radionuclides and x-ray therapy, and alkylating agents [23]. In the present study, only first cancers were included and thus therapeutic ionizing radiation and chemotherapy with alkylating agents is unlikely to be involved. The histology of bone cancers was one giant cell sarcoma and one hemangiosarcoma. This rare malignancy was not found in excess among the mining populations [20].

NHL

NHL is heterogeneous in aetiology and is classified into many histological types and by sites of origin. Many infectious agents, immune deficiencies, autoimmunity and high doses of ionizing radiation have been associated with NHL. Furthermore, other possible risk factors are farming, pesticides, organochlorines, besides host factors such as personal and family history of cancer and certain medical conditions [24]. A detailed knowledge of these risk factors among the population of the high-temperature geothermal areas or the reference areas is not at hand; however considerable agricultural activity and greenhouses were present in one of the areas. Previous study on pesticide users in Iceland did not find increased incidence of NHL [25].

NHL has not been associated with Rn exposure in miners [20].

Lung cancer

In the study from Rotorua the cancer concern in relation to the geothermal gas emissions were foremost cancers of the respiratory system [9] with some indication of elevated risk for lung cancer. In the present study the incidence of lung cancer was increased and more so among women, however, the confidence interval included unity. There is a general agreement on the interaction between Rn exposure and tobacco smoking on one hand and lung cancer risk on the other [14]. Breaking the smoking information from the Public Health Institute of Iceland [19] down on the geographical areas in this study showed the proportion of never smokers were fairly equally distributed among the studied populations, although highest in the high-temperature geothermal areas: 47.6% (based on 479 answers), warm areas: 45.4% (based on 16,187 answers), and cold areas 46.8% (based on 5,524 answers). Thus it seems unlikely that smoking habits were confounding the non-statistical significant increased risk for lung cancer.

BCC

Exposures to Rn and alpha radiation have previously been associated with BCC in a study of uranium miners [26]. In that study, surface contamination of the skin by Rn and its progeny was considered of importance, as the basal cell layer of the skin lies within the range of the alpha particles [26]. Ionizing radiation exposure and ultraviolet radiation from the sun are well known causes of BCC, and the interaction of these factors has been debated and partially rejected [27]. A recent ecological study in South West England showed an association of residential exposure to Rn and risk of squamous cell carcinoma, [28] and a previous study in the same setting also indicated an association of residential exposure to Rn and non-melanoma skin cancers. In that study, basal cell carcinoma was included among the non-melanoma skin cancers [29]. Arsenic in the water is unlikely to be a positive confounder for skin cancer in the present study, as geothermal hot water was not used as drinking water.

Excessive exposure to ultraviolet radiation is also not likely to be a confounder for the BCC in this study, as there is no corresponding increase in the rates of malignant melanoma or other skin cancers.

Other cancers

Many of the rarer cancer sites had few cases; however high HRs were observed for cancers of the nasal cavities, larynx, prostate, and for soft tissue sarcoma. The standardized incidence ratio for cancer of the nasal cavities was increased among the population of Rotorua, New Zealand [9]. The rates for prostate cancer and cancer of the thyroid gland were elevated, but the 95% CI for these cancer sites included unity.

Strength and limitations

To our knowledge, the follow up time in our cohort study is the longest of the populations in geothermal areas, thus far. The strength of the study is the use of comprehensive population registries and the universal use of personal identification numbers, which enabled accurate record linkage. For the cohort, it was thus possible to ascertain vital and emigration status through the National Registry and National Cause-of-Death Registry for all cohort members, and complete identification of cancer cases was ensured through the Icelandic Cancer Registry. The nation-wide cancer registry is virtually complete, with more than 95% of the diagnoses histologically confirmed, and the registry was used for case finding for both the exposed population and the reference populations [16].

BCC may be considered a special case, as these were all histologically verified and the incidence has increased dramatically through the years along with the incidence of malignant melanoma and other skin cancers in the Icelandic population. The increase may in part be attributed to more complete reporting to the cancer registry. In the study on skin cancer in South West England, the proportion of BCC to all non-melanoma skin cancers was 70%, [28] and the corresponding figure in the present study was 85% for the total cohort and 88% for the high-temperature geothermal areas.

The HR for all cancers combined was increased and so were HRs for several cancer sites, the rare sites showed for descriptive purposes. In no case when the HRs for certain cancer site were decreased were they followed by confidence intervals which included unity. So the whole pattern inclines towards increased risk for cancer in the high-temperature geothermal areas. Nevertheless concern may arise about a need of adjustment for multiple comparison, however, it has been maintained that these are not needed [30].

Both the present study and previous studies on populations in geothermal areas have been limited by a lack of individual exposure information on the cohort members in terms of mode and magnitude of the ground gas emission and the exact content of the hot water [8-10].

Census-based studies, including studies from Iceland, have in any case been widely used to evaluate occupational and socioeconomic determinates of cancers [18,31]. That type of study is often handicapped because of limited control on possible confounders. However, in the present study, we were able to adjust for educational level, lodging, and residential areas. On the other hand, we were only able to control indirectly for possible confounding from fertility rates, the mean age at the first birth, and smoking habits.

The excess rates of the different cancer sites found in this study seem hard to explain by single carcinogenic exposure specifically to geothermal gas emission, and that is the novelty of the study. The significant excess of BCC and breast cancer, and the suggested excess of cancer sites such as bone, nasal cavity, larynx, lung, thyroid gland, and of soft tissue sarcoma, all of these being radiation–sensitive cancers, indicate that Rn may contribute to the increased risk of cancer among the population in the high-temperature geothermal areas. According to IARC, Rn and its progeny are carcinogenic because of evidence of an increased risk for lung cancer [14] and IARC has stated that internalized radionuclides that emit alpha particles are carcinogenic to humans. The role of Rn seems not to be supported by the high rates found for pancreatic cancer and NHL, as cancers of these sites have infrequently been related to ionizing radiation. However, cytogenetic analysis in peripheral lymphocytes of persons exposed to increased levels of domestic Rn concentrations showed increased frequency of the translocation in stable cells compared with control individuals [32]. It was concluded in that study that the translocations were induced in the blood-forming tissue and then transmitted to the peripheral blood [32]. The respiratory tract has been considered the main target tissue of radon and its progeny; however, a part of the inhaled radon is absorbed into the blood and transported to all tissues of the body and deposited in higher concentrations in fatty tissues [14,32,33]. Various tissues, including bone marrow, are thus exposed to alpha particles [14].

In future studies of the geothermal areas, detailed information is needed on exposure on an individual level. These studies should also gather larger data and from different settings, and information on the length of residency in the geothermal areas should be obtained, as this can be used as a surrogate of the exposures among these populations. New studies are needed to confirm or refute the present findings.

Conclusions

More precise information on chemical and physical exposures are needed to draw firm conclusions from the findings. The significant excess risk of breast cancer and basal cell carcinoma of the skin and the suggested excess risk of other radiation sensitive cancers, calls for measurement of the content of the gas emissions and the hot water, which have been of concern in previous studies in volcanic areas. There are indications of an exposure-response relationship, as the risk was higher in comparison with the cold than with the warm reference area. Social status has been taken into account and data on reproductive factors and smoking habits show that these do not seem to explain the increased risk of cancers, however unknown confounding can not be excluded.

Abbreviations

BCC: Basal cell carcinoma; CI: Confidence intervals; CLL: Chronic lymphocytic leukemia, HR, Hazard ratio; IARC: International Agency for Research of Cancer; ICD-7: International classification of diseases, 7th revision; ICD-9: International classification of diseases, 9th revision; ICD-10: International classification of diseases, 10th revision; ICD-03: International classification of diseases for oncology; IQR: Inter quartile range; NHL: Non-Hodgkin's lymphoma; Non-CLL: Non-chronic lymphocytic leukaemia; p-yr: Person years; SD: Standard deviation.

Competing interests

Both authors declare that they have no competing interests.

Authors' contributions

AK and VR designed the study, planned the analysis, drafted the article, interpreted the conclusions, and agreeing on the final version. AK and VR initiated the study and VR obtained the funding and is the guarantor. All authors read and approved the final manuscript.

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Paper II

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Cancer incidence among population utilizing geothermal hot water: A census-based cohort study

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The aim of the study was to assess whether utilization of geothermal hot-water is associated with risk of cancer. The cohort from census was followed from 1981 to 2010 in nation-wide death and cancer registries. The moving apart of American-Eurasian tectonic plates, observed in Iceland, results in high volcanic activity. The definition of the study populations was based on geological information. The target population was inhabitants of communities located on bedrock younger than 3.3 million years, utilizing hot-water supply generated from geothermal wells since 1972. The two reference populations were inhabitants of communities without this hot-water supply located on areas with less volcanic/geothermal activity, and bedrock older than 3.3 million years. Hazard ratio (HR), and 95% confidence intervals (CI) were adjusted for age, gender, education, housing, reproductive factors and smoking. HR in the geothermal hot-water supply areas for all cancer was 1.15 (95% CI 1.05–1.25) as compared with nongeothermal areas. The HR for breast cancer was 1.40 (1.12–1.75), prostate cancer 1.61 (1.29–2.00), kidney cancer 1.64 (1.11–2.41), lymphatic and haematopoietic tissue cancers 1.45 (1.08–1.95), and for basal cell carcinoma (BCC) of the skin 1.46 (1.16–1.82). Positive exposure–response relations were observed between the risk of these cancers and the degree of volcanic/geothermal activity in the reference areas. Increased incidence of all cancers, breast, prostate, kidney cancer and BCC of the skin was found among the population utilizing geothermal hot-water for decades. More precise information on exposure is needed in future studies.

Epidemiology

Cancer risk among populations of volcanic areas has been studied in Rotorua, New Zealand, the volcanic islands of Azores, Portugal and Sicily, Italy. In some of these studies, an increased incidence of cancer has been found; however the cancer patterns were inconsistent.[1–3] These ecological studies have indicated an increase of nasal and lung cancers,[1] female breast cancer[2] or thyroid cancer[3] and they have suggested that the increase follows chronic exposure to various toxic ground gas emissions or various pollutants in the geothermal hot water that are usually abundant in these places.[4–6] The main component of these emissions are carbon dioxide (CO2), hydrogen sulphide (H2S), as well as radon (Rn), arsenic (As), lead (Pb) and mercury (Hg).[4–6] In a recent Icelandic study on residents of high-temperature geothermal areas, an increased incidence was found for all cancers, non-Hodgkin's lymphoma, pancreas and breast cancers, and basal cell carcinoma of the skin as compared with two reference populations.[7] The high-temperature geothermal areas in that study are located in the vicinity of central volcanoes, with many hot springs, fumaroles and erupting geysers. Frequent seismic activity ranges from easily perceived tremors to those under two on the Richter scale. For decades, hot water from drilled wells has been used for heating green houses, domestic heating, laundry, bathing, showering and washing dishes. Geothermal hot water is not used for drinking. The study results raise the question as to whether the cancer risk is associated with the utilization of the hot water rather than the location of the residences on volcanic soil.

The aim was to study whether utilization of geothermal hot water for heating and washing is associated with risk of cancer.

Key words: breast cancer, basal cell carcinoma of skin, prostate cancer, kidney cancer, cancer registry, geothermal hot-water
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Methods

Iceland is a volcanic island located in the North Atlantic Ocean on the boundary between the North American and Eurasian tectonic plates, which are moving apart at a rate of about 2 cm per year. Iceland is an anomalous part of the ridge where deep mantle material wells up and creates a hot spot of unusually great volcanic productivity and several geothermal fields.[8,9]

This is a population-based observational study. The source of data for the cohort was the 1981 National Census in Iceland. As the material has been dealt with in a previous study, only a brief description will be given here.[7] The census included information on personal identification number, gender, age, residency, education and the type of housing. The

What's new?
Residents of areas with high levels of geothermic and volcanic activity may be chronically exposed to toxic ground gas emissions and pollutants in geothermal hot water, potentially raising their risk of cancer. This study confirms suspected associations between increased cancer incidence and use of geothermal hot water for communities in Iceland that are located within regions where rifting of the American-Eurasian tectonic plates produces dramatic volcanic activity. The degree of exposure to volcanic/geothermal activity was positively linked to risk of breast, prostate, and kidney cancers, lymphatic and haematopoietic tissue cancers, and basal cell carcinoma of the skin.

cohort for this study was confined to people aged 5–64 years. The personal identification numbers were used in record linkage with the National Registry to obtain information, where applicable, on the date of emigration and with the National Cause-of-Death Registry to obtain information on vital status and, where applicable, the date of death. Both these registries are kept at Statistics Iceland. In this way, it was possible to ascertain the vital and emigration status for the entire cohort.

The Icelandic Cancer Registry is a nation-wide registry of all cases of cancer since 1955. The registry has virtually complete coverage and over 95% of the diagnoses are histologically confirmed.[10] Different versions of ICD were in use during the study period; however they were standardized by the registry to ICD-10. Basal cell carcinoma (BCC) has been registered in a special file at the cancer registry; it is not counted with the overall cancers, and is analyzed separately. The database of individuals in the census was linked to the Icelandic Cancer Registry by their personal identification numbers, and in that way we identified the cancer site, morphology and date of diagnosis.

The four-digit community code in the census was used to identify the populations living in communities with geothermal hot-water supply since 1972 or earlier, according to an overview of geothermal primary energy production for electricity generation and heating[11] published by the National Energy Authority. In these communities the hot water was used for domestic heating, laundry, bathing, showering and washing dishes, but not as drinking water. Included in this group of communities,[12] here called hot-water supply areas, are two small towns (Selfoss, and Husavik), and smaller rural districts (Reykjahreppur, Laugardalshreppur, Biskupstungnahreppur, Hrunamannahreppur and Skeidahreppur), and they are all located within the volcanic zone in the middle of the country, where the bedrock is less than 3.3 million-years-old.[8,9]

The two comparison populations, classified according to the community codes in the census, included residents of communities other than the hot-water supply areas identified above. The first of these comparison populations included residents living well outside of the volcanic zone, in what we call the cold reference area, where the bedrock is more than 3.3 million-years-old.[8,9] The population of the cold reference area is considered the main comparison population in the study. The second comparison population included those living within the volcanic zone, where the bedrock dates from different periods, but not exceeding 3.3 million years,[8,9] referred to here as the warm reference area. The population of the warm reference area did not have hot-water supply as early as 1972. The population of the cold reference area is the same as in the previous study.[7] However, the population of the warm reference area, compared with the previous study, is reduced in size by the population of the hot-water supply areas. The people in the warm reference area may or may not be living in the vicinity of geothermal fields, as these are spread out over the whole country. The population in the high-temperature geothermal area from the previous study is excluded from this study as well as the rest of the population living in the capital Reykjavik and in the south-west peninsula of Reykjanes. The reason for these exclusions is that the population of the high-temperature geothermal area was the exposed target population in the previous study, and the capital area and its adjacent south-west peninsula have, according to the cancer registry, had higher cancer incidence than other parts of the country for decades.[10] Geologically the Reykjavik and the Reykjanes areas would belong to the warm areas, and some of their communities have had hot-water supplies for many years.

The follow-up started at the day of the census, January 31, 1981, and continued to the date of emigration, or date of death, or the date of diagnosis of the first cancer, or December 31, 2010 (the end of the follow-up period), whichever occurred first. Survival for event-free proportions was shown for the exposed group and the two reference groups by Kaplan-Meier curves for all cancer sites.[13]The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI) for all cancers and selected cancer sites in time-dependent analyses.[14] Gender was introduced as a dichotomous variable, and age as a continuous variable in years. Educational level (basic, medium and academic education), was introduced as a categorical variable according to the previous classification in a census study[15] with two additional categories: one, unclassified for people under 20 years of age, who had not yet attained their full education level, and one missing educational information for individuals who did not indicate their education in the census. Type of residence, single-family house or other type of residence, was introduced as a dichotomous variable. The

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exposed population living in the hot-water supply areas was compared with the other two populations (warm reference area and cold reference area) in separate analyses. We did several calculations in the model: crude comparison without any adjustments, comparison with adjustment for age and gender only, and with adjustment for age, gender, educational level and housing. These three models had nearly identical results. Only the results with all these adjustments and additionally adjusted for smoking (see later) are presented here. All cancer sites with two or more cancer cases are shown in the tables for completeness, and sites with one case are not shown. Separate analyses were done after dividing the material by gender and into groups of individuals who were 20 years of age or older at the time of the census and those who were under 20 years of age, to investigate possible bias from childhood cancer.

The age of women at first birth is the most important possible confounder in breast cancer studies of this design.[16] Information on reproductive factors was not available from the census. However, data was obtained from Statistics Iceland[12] on the exact number of women per age at first birth for the years 1991–1995, broken down by community codes and thus a sample of the birth age history for the respective communities, however unknown on individual basis. From this information, reproductive factor codes were calculated for number of women who had given first birth before 25 years of age, divided by number of women who had given first birth after 25 years of age, according to 24 community areas, and these estimates were allocated to each woman regardless of age accordingly to the communities in the study population in the hot-water supply, cold reference and warm reference areas. The codes on age at first birth (<25 and 25+) were introduced as a continuous variable in the Cox model in separate analyses for breast cancer and gynaecological cancers.

Information on smoking was not collected in the census and thus not available on an individual level. Since 1985, the Public Health Institute of Iceland has collected results from annual surveys on smoking habits among random samples of the population according to gender and postal codes.[17] Raw data on smoking surveys during 1991–1995 were obtained from the institute for the purpose of this study. The postal codes were translated to 22 community areas to fit into the community codes in the census and rates for never-smokers were calculated for each community. These estimated never-smoker rates were assumed for inhabitants of the study areas, and allocated to the individuals of the respective communities regardless of age, but broken down on gender, and introduced as a continuous variable in the Cox model, taking all cancers and cancer sites into consideration.

The statistical analyses were performed using the PASW (SPSS) software version 18, and Microsoft Excel 2007.

The National Bioethics Committee (VSNb2010060005/03.1) and the Data Protection Commission (2010060524Þ PJ/-) approved the study.

Results

The national census in 1981 included nearly every one living in Iceland at that time, as the individuals aged 5–64 years in the census numbered 184,114, and the number of persons in the same age range in the National Registry was 185,610; thus 99.2% were included in the census.

The baseline characteristics in the three study populations: the hot-water supply areas, the warm reference area, and cold reference area are shown in Table 1. The total number of individuals in the study was 73,309 and altogether there were 1 866,079 person-years. The average follow-up was 24.9 years and a total of 7,505 cases of first cancer were identified through the cancer registry. The gender and age distributions between the populations were fairly equal.

Figure 1 shows the results of the Kaplan–Meier survival analysis that illustrates the time until first cancer reported to the Cancer Registry in the hot-water supply area and the cold reference area. Inhabitants of the hot-water supply area represented a greater proportion of people diagnosed with cancer than inhabitants of the cold reference area at each time point, and curves never crossed during the study period.

Figure 2 shows the results of the Kaplan–Meier survival analysis that illustrates the time until first cancer reported to the Cancer Registry in the hot-water supply area and the warm reference area. A greater proportion of inhabitants of the hot-water supply area were diagnosed with cancer than for inhabitants of the warm reference area at each time point, and here the curves are closer but they never crossed during the study period.

Table 2 shows the number of all cancers, and selected cancer sites in the hot-water supply areas, and the HR and 95% CI, adjusted for age, gender, education, type of housing and smoking habits. During the follow up, 673 cases of cancers were diagnosed among men and women in the hot-water supply areas and the HRs for all sites were 1.10 (95% CI 1.01–1.20) and 1.15 (95% CI 1.05–1.25), compared with the warm reference area and the cold reference area respectively. The HRs for breast cancer were 1.28 (95% CI 1.04–1.59), and 1.40 (95% CI 1.12–1.75) compared with the reference areas. The HRs for prostate cancer were 1.48 (95% CI 1.21–1.82), and 1.61 (95% CI 1.29–2.00). The HRs for kidney cancer were 1.51 (95% CI 1.05–2.18), and 1.64 (95% CI 1.11–2.41). The HRs for brain and central nervous system cancer were 0.56 (95% CI 0.32–0.98), and 0.64 (95% CI 0.36–1.13). The HR for lymphoid and haematopoietic tissue cancer were 1.34 (95% CI 1.01–1.78), and 1.45 (95% CI 1.08–1.95). The HRs for several cancer sites increased, but these were based on few cases with wide confidence intervals. The HRs for the 110 cases of BCC in the hot-water supply areas were 1.24 (95% CI 1.01–1.54), and 1.46 (95% CI 1.16–1.82) compared with the warm reference area and the cold reference area respectively, shown in the lowest row of Table 2. For the following sites there was single cancer: larynx (C32), vulva (C51), vagina (C52), penis (C60), other and unspecified urinary organs (C68) and craniopharyngeal duct (C75.2) in the hot-water supply area and these are not shown in Table 2.

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Table 1. Baseline characteristics in the hot-water supply areas and different reference areas according to census 1981

	Hot-water supply areas *N* (%)	Warm reference area *N* (%)	Cold reference area *N* (%)
Number of people	6,014 (100)	44,864 (100)	22,431 (100)
Gender			
Men	3,126 (52.0)	23,305 (51.9)	11,929 (53.2)
Woman	2,888 (48.0)	21,559 (48.1)	10,502 (46.8)
Age, year			
Mean ± SD	27.96 ± 16.11	28.14 ± 16.30	28.06 ± 16.20
Median, IQR (0.25; 0.75)	25 (15; 40)	25 (15; 40)	25 (15; 39)
Education			
Basic education	1,461 (24.3)	12,370 (27.6)	6,565 (29.3)
Medium education	1,660 (27.6)	11,754 (26.2)	5,665 (25.3)
Academic education	482 (8.0)	3,171 (7.1)	1,428 (6.4)
Unclassified	2,343 (39.0)	17,061 (38.0)	8,481 (37.7)
Missing	68 (1.1)	508 (1.1)	292 (1.3)
Housing			
Single family home	4,525 (75.2)	29,236 (65.2)	17,343 (77.3)
Other type of house	1,489 (24.8)	15,628 (34.8)	5,088 (22.7)
Region			
Urban regions ≥ 500 individuals	4,726 (78.6)	30,554 (68.1)	12,839 (57.2)
Rural regions < 500 individuals	1,288 (21.4)	14,310 (31.9)	9,592 (42.8)

Abbreviations: SD standard deviation, IQR interquartile range.

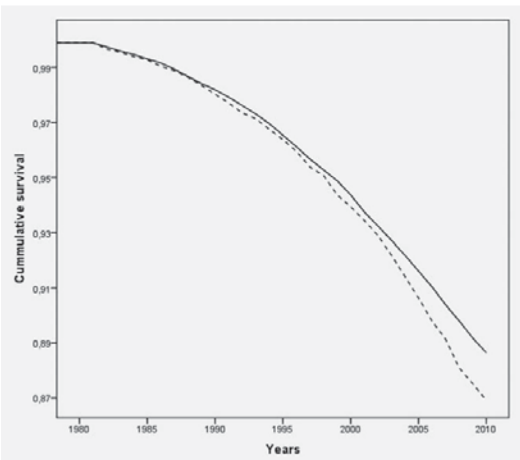

Figure 1. Kaplan-Meier estimates of event free proportion for first diagnosis of cancer since the census 1981, dashed line indicate population in hot-water supply areas, and black line population in cold reference area. Log-rank test: $p = 0.001$.

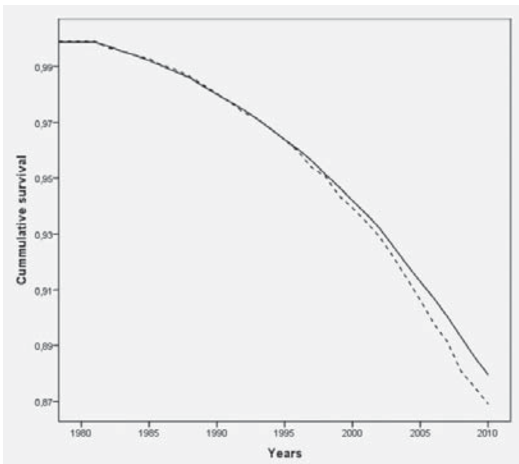

Figure 2. Kaplan-Meier estimates of event free proportion for first diagnosis of cancer since the census 1981, dashed line indicate population in hot-water supply areas, and black line population in warm reference area. Log-rank test: $p = 0.041$.

In the separate analysis for breast cancer and gynaecological cancers with adjustments for reproductive factors without adjustments for smoking the HR for breast cancer was 1.37 (95% CI 1.03–1.82), for cervical cancer 0.53 (95% CI 0.16–1.78), uterine cancer 1.31 (95% CI 0.65–2.64) and for ovarian cancer 0.81 (95% CI 0.38–1.74) compared to the cold

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Table 2. Number of all cancers and selected cancer sites among men and women combined in the hot-water supply areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits

	Hot-water supply areas	Warm reference area			Cold reference area		
	p-yr 152,509	p-yr 1 141,930			p-yr 571,450		
Cancers (ICD-10)	No of cancers	No of cancers	HR	95%CI	No of cancers	HR	95%CI
All sites (C00-C97 and D45-D47)	673	4,641	**1.10**	**1.01–1.20**	2,191	**1.15**	**1.05–1.25**
Lip, oral cavity, and pharynx (C00-C14)	13	85	1.02	0.56–1.87	36	1.45	0.76–2.76
Oesophagus (C15)	11	57	1.37	0.70–2.69	25	1.76	0.85–3.64
Stomach (C16)	20	183	0.82	0.51–1.32	101	0.77	0.47–1.24
Small intestine (C17)	3	10	4.43	0.94–20.77	4	2.41	0.60–9.61
Colon, rectum, and anus (C18-C21)	60	398	1.19	0.89–1.57	193	1.15	0.86–1.54
Bile and liver (C22-C24)	6	65	0.71	0.30–1.67	29	0.82	0.34–2.00
Pancreas (C25)	16	104	1.23	0.71–2.13	45	1.32	0.74–2.34
Lung and bronchus (C33-C34)	56	505	0.84	0.63–1.12	263	0.80	0.60–1.06
Bone (C40-C41)	2	19	0.71	0.16–3.18	5	1.42	0.27–7.33
Melanoma (C43)	19	123	1.07	0.65–1.79	49	1.48	0.86–2.53
Other cancer of skin (C44)	16	144	0.85	0.50–1.46	59	1.04	0.60–1.81
Peritoneum (C48)	2	4	1.71	0.31–9.50	7	3.45	0.63–18.85
Soft tissue sarcoma (C49)	3	33	0.71	0.21–2.39	15	0.69	0.20–2.40
Breast (C50)	112	622	**1.28**	**1.04–1.59**	280	**1.40**	**1.12–1.75**
Cervix uteri (C53)	9	78	0.73	0.36–1.49	29	1.06	0.50–2.24
Uterus (C54-C55)	18	98	1.49	0.87–2.54	46	1.41	0.81–2.44
Ovary (C56-C57)	12	126	0.70	0.38–1.30	58	0.73	0.39–1.36
Prostate (C61)	117	668	**1.48**	**1.21–1.82**	308	**1.61**	**1.29–2.00**
Testis (C62)	2	37	0.40	0.10–1.71	22	0.35	0.08–1.50
Kidney (C64-C66)	38	205	**1.51**	**1.05–2.18**	87	**1.64**	**1.11–2.41**
Bladder (C67)	31	204	1.10	0.75–1.63	111	1.08	0.72–1.61
Brain and central nervous system (C70-C72, C75.1 and C75.3)	14	199	**0.56**	**0.32–0.98**	84	0.64	0.36–1.13
Thyroid gland (C73)	17	117	1.18	0.69–2.01	60	1.01	0.59–1.74
Cancer without specification of site (C80)	8	102	0.69	0.33–1.44	52	0.60	0.29–1.27
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	62	337	**1.34**	**1.01–1.78**	167	**1.45**	**1.08–1.95**
Hodgkin's lymphoma (C81)	4	32	0.74	0.26–2.13	11	1.44	0.44–4.69
Non-Hodgkin's lymphoma (C82-C85)	21	109	1.55	0.95–2.54	56	1.53	0.91–2.56
Immunoproliferative diseases (C88)	4	21	1.42	0.46–4.38	7	2.23	0.65–7.67
Multiple Myeloma (C90)	14	67	1.55	0.84–2.85	34	1.54	0.82–2.88
Leukaemia (C91-C95 and D45-D47)	19	106	1.25	0.75–2.08	58	1.30	0.77–2.21
Chronic lymphocytic leukaemia (CLL)(C91.1)	9	31	2.00	0.91–4.40	21	1.85	0.84–4.11
Non-CLL (C91-C95 and D45-D47, except C91.1)	10	75	0.94	0.47–1.85	37	1.04	0.51–2.10
Not included in all cancers							
	p-yr 155,740	p-yr 1 164,480			p-yr 581,772		
Basal cell carcinoma of the skin	110	617	**1.24**	**1.01–1.54**	271	**1.46**	**1.16–1.82**

Statistically significant HRs are bolded. Abbreviation: p-yr, person years.

reference area. These HRs were similar as the HRs for these cancer unadjusted for reproductive factors, indicating similar average age at first birth in the areas in the study.

Among men, 351 cases of cancer were found in the hot-water supply areas, and the HR for all cancers was 1.22 (95% CI 1.08–1.37), for prostate cancer 1.61 (95% CI 1.29–2.00),

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Table 3. Number of all cancers and selected cancer sites among men and women separately in the hot-water supply areas areas, hazard ratio (HR), 95% confidence intervals (CI) according to comparison with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits

	Hot-water supply areas	Warm reference area			Cold reference area		
	p-yr 78,519	p-yr 588,484			p-yr 300,266		
Cancers (ICD-10)	No of cancer	No of cancer	HR	95%CI	No of cancer	HR	95%CI
Men							
All sites (C00-C97 and D45-D47)	351	2,447	**1.14**	**1.01–1.27**	1,151	**1.22**	**1.08–1.37**
Oesophagus (C15)	10	44	1.60	0.79–3.27	16	**3.34**	**1.35–8.26**
Prostate (C61)	117	668	**1.48**	**1.21–1.82**	308	**1.61**	**1.29–2.00**
Kidney (C64-C66)	24	125	1.44	0.92–2.28	54	**1.76**	**1.08–2.86**
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	33	204	1.24	0.84–1.81	104	1.29	0.87–1.93
Non-Hodgkin's lymphoma (C82-C85)	12	64	1.52	0.80–2.90	41	1.16	0.60–2.24
Not included in all cancers							
	p-yr 79,925		p-yr 598,652			p-yr 305,053	
Basal cell carcinoma of the skin	49	276	1.29	0.94–1.77	123	**1.46**	**1.05–2.04**
	p-yr 73,990		p-yr 553,446			p-yr 271,184	
Women							
All sites (C00-C97 and D45-D47)	322	2,194	1.08	0.96–1.22	1,040	1.09	0.96–1.23
Breast (C50)	109	613	**1.27**	**1.02–1.58**	275	**1.38**	**1.11–1.73**
Kidney (C64-C66)	14	80	1.69	0.92–3.10	33	1.49	0.79–2.81
Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	29	133	1.48	0.96–2.26	63	**1.66**	**1.06–2.58**
Non-Hodgkin's lymphoma (C82-C85)	9	45	1.57	0.73–3.38	15	**2.50**	**1.07–5.83**
Not included in all cancers							
	p-yr 75,816		p-yr 565,827			p-yr 276,719	
Basal cell carcinoma of the skin	61	341	1.21	0.91–1.61	148	**1.43**	**1.06–1.93**

Statistically significant HRs are bolded. Abbreviation: p-yr, person years.

for kidney cancer 1.76 (95% CI 1.08–2.63) and for BCC HR was 1.46 (95% CI 1.05–2.04) adjusted for age, education, housing and smoking in comparison with the cold reference area, see Table 3. Among women, 322 cases of cancer were found in the hot-water supply areas, and the HR for breast cancers was 1.38 (95% CI 1.11–1.73), for lymphoid and haematopoietic tissue cancer HR was 1.66 (95% CI 1.06–2.58), for non-Hodgkin's lymphoma 2.50 (95% CI 1.07–5.83) and for BCC HR was 1.43 (95% CI 1.06–1.93) adjusted for age, education, housing and smoking in comparison with the cold reference area, see Table 3.

When the material was restricted to those 20 years of age and older in the census, there were altogether 636 cancer cases in the hot-water supply areas. In this older part of the cohort, comparison of the hot-water supply areas with the cold reference area gives similar HRs as in the total exposed cohort. HR for all cancer sites was 1.15 (95% CI 1.06–1.27), for breast cancer 1.41 (95% CI 1.12–1.78), for prostate cancer 1.62 (95% CI 1.30–2.02), for kidney cancer 1.65 (95% 1.12–2.44), for lymphatic and haematopoietic tissue cancer 1.48 (95% CI 1.09–2.02) and for BCC of the skin, the HR was 1.55 (95% CI 1.23–1.95) adjusted for age, gender, education, type of housing and smoking habits. HRs for other cancer sites did not significantly deviate from unity.

In the analysis restricted to those less than 20 years of age at the time of the census, there were 37 cancers cases in the hot-water supply areas. Incidences for all cancer were increased in the hot-water supply areas compared to the cold reference area, but not to a statistically significant degree. None of the HRs in this younger part of the cohort were significantly elevated.

Discussion

The present study showed an association between residence in areas where geothermal hot water had been used for decades and increased risk for all cancers due specially to a higher rate for breast, prostate and kidney cancer, and particularly for BCC of the skin. These findings confirm recent reports on increased risk for breast cancer and BCC of the skin among the population of high-temperature geothermal areas.[7]

The increase for breast cancer is consistent with findings among the female population in a geothermal area of Furnas, Azores.[2] In the present study, adjustments were made for social variables (educational level and type of housing) registered in the census, and estimates of age at first birth, as well as smoking habits.

Breast cancer

In this study, we were able to adjust for age at first birth, one of the main known risk factors for breast cancer.[16] Previous studies among populations of geothermal areas suggested that the increased risk of breast cancer may be partially explained by gas emissions, trace elements and Rn exposure.[2] Lack of exposure measurements precludes such reflections on the possible causes of the increased breast cancer rate in the present study. Studies on exposure to Rn and breast cancer risk among women are not available, the studies on Rn-exposed mining populations did not include female workers,[18] and the studies on residential exposure to Rn and cancer risk were of case–control design and concentrated on lung cancer.

Prostate cancer

There was an increased rate of prostate cancer in the exposed cohort as compared to both reference areas. The established risk factors for prostate cancer are age, area of residence (according to migration studies), ethnic background and family history and the aetiology is claimed to be extensively studied.[19] In the present study age is taken into consideration in the calculations and the populations are homogenous Caucasians. Several studies have evaluated nutritional aetiology of prostate cancer, however yet not reached definitive conclusions[19] and an Icelandic study found an association between milk intake in early life and risk of advanced prostate cancer.[20] That study was confined to a population that had been resident in the capital area at least since 1967; however, the capital area was excluded from this study.[20] Prostate cancer incidence was increased in an earlier study on high-temperature geothermal areas, albeit not significantly.[7]

Kidney cancer

The incidence of kidney cancer was increased for both genders combined and among men only in comparison with warm and cold reference areas, with and without adjustment for smoking habits. Increased kidney cancer has not been found in previous studies on geothermal areas or in the study of high-temperature geothermal areas.[7] Kidney cancer has been associated with smoking, obesity and hypertension[21] and in this study, we were only able to control for smoking.

NHL

NHL is clinically and etiologically heterogeneous and classified into different histological types.[22] Various viral infections, immune deficiencies, autoimmunity and high-dose ionizing radiation have been associated with NHL. Other risk factors are farming, pesticides, organochlorines, beside host factors such as personal and family history of cancer and certain medical conditions. Some of the communities in the hot-water supply areas were agricultural districts with greenhouses, although that involved only a minority of the population. The association of reproductive factors with NHL is not clear; however a Swedish study has shown a protective effect of parity,[23] while an Italian study did not support any protection of reproductive factors on the risk of NHL.[24] In the present study, the risk of NHL increased when adjusted for age at first birth.

BCC

The majority of skin cancers are considered to be attributable to sunlight and ultraviolet radiation.[25] Exposure to ultraviolet radiation is not likely to explain the increase in risk of BCC, as no corresponding significant increase in malignant melanoma or other skin cancer is observed. Arsenic content in water, both drinking water and the geothermal water in Iceland, is low,[26,27] so it is unlikely to be a positive confounder for skin cancer in the present study. Ionizing radiation is a well-known cause of BCC[28,29] and one study of miners has indicated that dermal exposure of Rn is a risk factor for BCC.[30] Nonmelanoma skin cancer and BCC have also been associated with domestic Rn exposure in ecological studies.[31,32]

Brain and central nervous system

There was a decrease rate of cancer of brain and central nervous system in the hot-water supply area as compared to the other areas. An explanation of this reduction is not at hand.

Strengths and limitations

To the strength of the study we count the universal use of personal identification numbers in the census, and the comprehensive population registers, which enabled accurate record linkage and thus exact identification of the cancer cases in the exposed as well as the reference populations. In the cancer registry, more than 95% of the diagnoses are histologically verified, and in the case of BCC all diagnoses are histologically confirmed.

On account of exact population-based information[12] on the age of mothers at first birth, a community-based code on the reproductive factor was calculated (women giving first birth at age <25 and $25+$), and these were introduced into the Cox model, so it was possible to adjust the HR for breast cancer and gynaecological cancers. In a similar manner, information concerning smoking habits on a community level was available from population-based surveys,[17] and that made adjustment for smoking possible in the final model.

Screening with mammography has been offered to all women 40–69 years of age since 1987, with no indication of differences in participation according to regions.[10] Detection bias regarding breast cancer is thus unlikely. The populations in the study were located, at the time of the census, outside the capital area, however, it is the population of the capital area which have easy access to health care and specialist services rather than those in the countryside. Systematic screenings have not been set up or recommended for prostate or skin cancer in these populations.

As in the previous study on residents of high-temperature geothermal areas,[7] the present study is limited by lack of individual exposure information on the mode and magnitude of ground gas emissions and components of the drinking water, as well as the content of the hot water. Previous studies on populations in geothermal areas[1–3] were of an ecological nature, as is this study, and measurement of gas emissions was published later.[4–6] The sporadic information on the hot-water and drinking water contents have not been investigated for the purpose of this study. However, they indicate low, but nevertheless varying concentrations of As and Rn.[26,27,33,34]

The increased rates of several cancer sites confirmed in this study is difficult to explain by an exposure to a single carcinogenic factor, so one may suspect a more complex situation. However, if Rn in the geothermal water plays a role the heaviest exposure may occur while showering or bathing when the hot-water is aired in rather small rooms. This scenario may explain the excess of BCC as according to previous studies on Rn exposed miners and residence in South West England,[30,32] the exposure were thought to be due to dermal contamination. Higher proportion of BCC located on trunk than on face and head among the population of the hot-water supply area than among the comparison populations support the significance of the dermal contamination. The Rn has to be internalized[35] to be able to contribute to the risk of other cancer than skin cancer in this study. A part of inhaled Rn is considered to be absorbed into the blood and transported to all tissue of the body and may accumulate in fatty tissues.[35–37] Because of lack of measurement of Rn in the present settings the role of Rn must be considered merely speculative. It is also worth mentioning that the majority of the epidemiological studies on the carcinogenesis of Rn have focused on male miners and dust exposure of the lungs,[18,35] while the target population in the present study consist of male and female individuals sustaining exposure to gas emission.

Future studies ought to concentrate on environmental factors such as ambient air pollutant in the volcanic fields, diet, drinking water and hot water components including concentration of heavy metals and the possibility of radionuclides as many social and lifestyle factors are already controlled for.

The concept population attributable fraction assumes causality and it may be premature to assume that in the present setting,[13] however, the attributable risk was 57.9 per 10^5, and the population attributable fraction was 13. This discussion is nevertheless important, as millions of people worldwide live within volcanic-geothermal areas.[38]

Conclusion

The significant excess risk of all cancers, breast and prostate cancers, and the combined cancers of the lymphoid and haematopoietic tissue, and BCC of the skin confirmed the results of the previous study from high-temperature geothermal areas. As in the earlier study, an exposure-response relationship was observed for these cancers. Adjustment was made for individual social-related variables, as well as for reproductive factors and smoking habits on the community level. Further studies are needed of the gas and radon emissions occurring in geothermal and volcanic areas and the content of the hot water utilized by those living in these areas.

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Paper III

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ORIGINAL ARTICLE

Cancer mortality and other causes of death in users of geothermal hot water

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ABSTRACT

Background. Residents of geothermal areas have increased incidence of non-Hodgkin's lymphoma, breast, prostate, and kidney cancers. The aim was to study whether this is also reflected in cancer mortality among the population using geothermal hot water for space heating, washing, and showering.
Methods. The follow-up was from 1981 to 2009. Personal identifier of those 5–64 years of age was used in record linkage with nationwide death registry. Thus, vital and emigration status was ascertained. The exposed population was defined as inhabitants of communities with district heating generated from geothermal wells since 1972. Reference populations were inhabitants of other areas with different degrees of volcanic/geothermal activity. Hazard ratio (HR) and 95% confidence intervals (CI) were adjusted for age, gender, education, housing, reproductive factors and smoking habits.
Results. Among those using geothermal water, the HR for all causes of death was 0.98 (95% CI 0.91–1.05) as compared with cold reference area. The HR for breast cancer was 1.53 (1.04–2.24), prostate cancer 1.74 (1.21–2.52), kidney cancer 1.78 (1.03–3.07), and for non-Hodgkin's lymphoma 2.01 (1.05–3.38). HR for influenza was 3.36 (1.32–8.58) and for suicide 1.49 (1.03–2.17).
Conclusion. The significant excess mortality risk of breast and prostate cancers, and non-Hodgkin's lymphoma confirmed the results of similarly designed studies in Iceland on cancer incidence among populations from high-temperature geothermal areas and users of geothermal hot water. The risk is not confined to cancers with good prognosis, but also concerns fatal cancers. Further studies are needed on the chemical and physical content of the water and the environment emissions in geothermal areas.

Air pollution and its impact on human health have been considered a serious problem in active volcanic areas. Millions of people globally live within volcanic-geothermal areas [1]. Toxic emissions from volcanic and geothermal areas include carbon dioxide (CO_2), sulphur dioxide (SO_2), hydrogen chloride (HCl), hydrogen fluoride (HF), hydrogen sulphide (H_2S), carbon monoxide (CO), radon (Rn) and various trace elements [2–6]. Unlike emissions of hazardous air pollutants during eruptions, ground gas emissions from geothermal fields are continuous and communities in these areas may be chronically exposed to elevated gas concentrations.

The main components of the gas emissions from the geothermal fields and fumaroles in Iceland are CO_2, H_2S, SO_2, and hydrogen (H_2) and the information available from Icelandic settings indicate the presence of traces of hazardous elements in the geothermal water including arsenic (As) (1–2 ppb), mercury (Hg) (0.05 ppb), and Rn (3–100 Bq/l), i.e. in low quantities, but in varying concentrations [7–10]. The geothermal hot water, from deep drilled wells (down to 800 m), has been piped into power plants, industries, green houses and domestic houses and used for heating, laundry, bathing, showering and washing dishes [11]. The faint rotten egg odour of H_2S breaking out from showers, spas and swimming pools are frequently perceived by foreign visitors, while the local population seem to have acclimatised the smell. Approximately 90% of all houses and swimming pools are at present heated with geothermal water and 12% of the electricity is generated from geothermal power plants in Iceland [11]. The geothermal water is not used for drinking water because it is bad tasting and foul smelling.

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Long-term mortality studies on populations living on geothermal fields or in volcanic areas are rare. A mortality study in New Zealand's Rotorua geothermal area showed an elevated ratio for diseases of the respiratory system; however, that finding was possibly confounded by ethnicity [12]. The study in Rotorua did not include mortality from cancer [12]. An ecological study of the population in geothermal areas of Tuscany, Italy [13] showed excess mortality among males for respiratory diseases, in particular due to pneumoconiosis, including silicosis, and an excess of tuberculosis was also found, thus possibly indicating significant industrial exposure, besides geothermal emissions.

Previous studies on the incidence of cancer among populations in geothermal or volcanic areas have been inconsistent [14–16], however a pattern has emerged from two Icelandic studies showing increased incidence of non-Hodgkin's lymphoma, breast, and prostate cancers, and basal cell carcinoma of the skin [17,18].

Many of the tumours found in excess in the incidence studies [14,16–18] have good prognosis, and are possibly subject to detection bias. Mammography screening and prostate-specific antigen testing may produce overdiagnosis [19,20] of these cancers. Moreover, risk factors for advanced or lethal breast and prostate cancers may be different from those for indolent cancers [21,22]. These debatable questions call for assessment of the risk of cancer mortality among populations in geothermal areas.

The aim was to study cause-specific mortality, with special focus on cancer mortality, in geothermal areas where the population has been using geothermal hot water for space heating, bathing and washing for decades.

Methods

Iceland is located in the middle of the North Atlantic Ocean on the Mid-Atlantic Ridge where the North American and Eurasian tectonic plates move apart. These movements can be observed in Iceland, which gets 2 cm longer from east to west each year, and Iceland has great volcanic activity and several geothermal fields [23,24].

The source of data for this cohort study was the 1981 National Census in Iceland. The material has been described in previous studies, so a short outline will be given here [17,18].

The census included information on personal identification number, gender, age, residency, education, and type of housing. The cohort included people aged 5–64 years. Personal identification numbers were used in record linkage with the National Registry to obtain information, where applicable, on the date of emigration and with the National Cause-of-Death Registry to obtain information on vital status and, where applicable, the date and the cause of death according to death certificates. These registries are kept at Statistics Iceland. Through this procedure it was possible to ascertain the vital and emigration status for the entire cohort.

The European shortlist [25] was used to define the causes of death and to standardise these to ICD-10 [25], except for the cancers, where the same categories were used as in previous studies also complying with ICD-10 [17,18].

The age of the bedrock played a pivotal role in the definition of the populations studied (Figure 1). The four-digit community code in the census was used to identify the populations living in communities

Figure 1. Map of Iceland showing the age of the bedrock, dark area: age of bedrock less than 0.8 million years, grey area: age of bedrock 0.8–3.3 million years, light grey area: age of bedrock 3.3–15 million years, and white area: glaciers. Modified with permission from Iceland GeoSurvey – ÍSOR.

with geothermal heating since 1972 or earlier, according to an overview of geothermal primary energy production [11,26]. In these communities the hot water was used for domestic heating, laundry, bathing, showering, and washing dishes, and in spas and swimming pools, but not as drinking water. These are the communities dealt with in previous studies [17,18], here called geothermal heating areas. They included three small towns, two of these were inland, Selfoss (8100), Hveragerdi (8716), and one was coastal, Husavik (6100), and six rural districts Reykjahreppur (6610), Skutustadahreppur (6607), Laugardalshreppur (8712), Biskupstungnahreppur (8711), Hrunamannahreppur (8710), and Skeidahreppur (8708) (Figure 2), and they are all located within the volcanic zone in the middle of the country, where the bedrock is less than 3.3 million years old (Figure 1) [23,24].

The two comparison populations were identified by the community codes in the census [26] according to the age of the bedrock [23,24] and without geothermal heating system as old as 1972 [11]. The main reference area, the cold area, was located in the west and east parts of the country where the bedrock is more than 3.3 million years old, and the warm reference area was located in the middle of the country, where the age of the bedrock is 0.8–3.3 million years old. These reference areas are the same as in a previous study [18] (Figure 2).

The populations in the capital Reykjavik and in the south-west peninsula of Reykjanes were excluded from the study, as the population of the capital area and its adjacent south-west peninsula has had higher cancer incidence than the rest of the country in the Cancer Registry since the beginning of the registry [27], a well-known phenomenon in cancer registries, sometimes called the capital effect.

The follow-up started on the day of the census, 31 January 1981, and continued to the date of emigration, or date of death, or 31 December 2009 (the end of the follow-up period), whichever occurred first.

Survival for the event-free proportion was shown for the exposed group and the two reference groups combined by Kaplan-Meier curves for breast, and prostate cancer mortality, non-Hodgkin's lymphoma, and suicides [28].

The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI) for all causes of death and selected

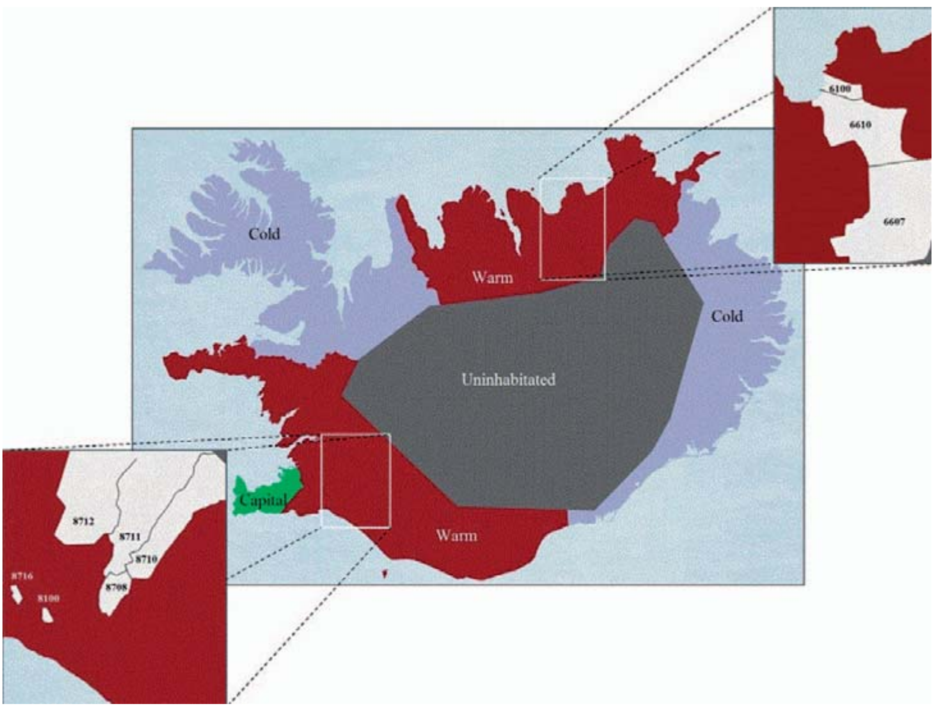

Figure 2. Map of Iceland showing the study areas: 1) Geothermal heating area, two enlarged parts with community codes, 2) Cold reference area, 3) Warm reference area, 4) Capital and South West area, and 5) Uninhabited area. Modified with permission from National Land Survey of Iceland.

causes of death [29]. Gender was introduced as a dichotomous variable, and age as a continuous variable in years. Educational level (basic, medium and academic education), was introduced as a categorical variable according to the previous classification in a census study [30] with two additional categories: one, unclassified for people under 20 years of age, who had not yet attained their full education level, and another missing educational information to include individuals who did not indicate their education in the census. Type of residence, single-family house or other type of residence, was introduced as a dichotomous variable.

The exposed population living in the geothermal heating area was compared with the other populations (warm reference area and cold reference area) in separate analyses. Several calculations were done in the model: crude comparison without any adjustments, comparison with adjustment for age and gender only, and with adjustment for age, gender, educational level, housing, and smoking. These models had nearly identical results. Only the results with all these adjustments are presented here. Further adjustment for urban/rural region did not change the results and were omitted from the model. Separate analyses were done after dividing the material by gender, and then the cold and warm reference populations were combined into one comparison population, and into groups of individuals who were 20 years of age or older at the time of the census, and those who were under 20 years of age.

Information on smoking was not collected in the census and thus not available on an individual level. Since 1985, the Public Health Institute of Iceland has collected results from annual surveys on smoking habits among random samples of the population according to gender and postal codes [31]. Raw data on smoking surveys during 1991 to 1995 were obtained from the institute for the purpose of this study. The postal codes were translated to 22 community areas to fit into the community codes in the census and rates for never-smokers were calculated for each community and gender. These estimated never-smoker rates were assumed for inhabitants of the study areas, and allocated to the individuals of the respective communities regardless of age, but broken down by gender, and introduced as a continuous variable in the Cox model.

Information on reproductive factors was not available from the census. The most important reproductive factor, age at first birth [32], was estimated according to information from Statistics Iceland [26] with calculation of codes on age at first birth (<25 and $25+$) by a method described in the previous publication [18]. In order to adjust for possible confounding, these community codes were introduced as a continuous variable in the Cox model in a separate analysis for breast cancer mortality.

The statistical analyses were performed using the PASW (SPSS) software version 18, and Microsoft Excel 2007.

The National Bioethics Committee (VSNb2010060005/03.1) and the Data Protection Commission (2010060524ÞPJ/--) approved the study.

Results

The national census in 1981 used in the study covered, according to the National Registry, 99.2% of the population aged 5–64 years [18,26]. During the follow-up, a total of 10 102 persons had died, 6132 men and 3970 women.

The baseline characteristics in the three study populations: Geothermal heating area and the reference areas (warm area, and cold area) are shown in Table I. The proportion of never-smokers in the geothermal heating area was 43.8, it was 46.9 in the warm reference area, and 44.7 in the cold reference area.

Figure 3 shows the results of the Kaplan-Meier analyses; these demonstrate the time until deaths occur due to breast and prostate cancer, non-Hodgkin's lymphoma, and suicide in the geothermal heating area and the combined reference areas.

The number of all causes of death, and selected causes of death for the genders combined in the three areas, the HR, and 95% CI, adjusted for age, gender, education, type of housing, and smoking habits are shown in Supplementary Table I (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.923113). During the follow-up, 996 deaths were among men and women in the geothermal heating area and the HRs for all causes of death were 1.01 (95% CI 0.94–1.08) compared with the warm reference area, and 0.98 (95% CI 0.91–1.05) compared with the cold reference area. The HRs for all cancers were 1.05 (95% CI 0.94–1.18), and 1.03 (95% CI 0.92–1.17) compared with the reference areas. The HRs for breast cancer were 1.48 (95% CI 1.03–2.12), and 1.53 (95% CI 1.04–2.24). The HRs for prostate cancer were 1.88 (95% CI 1.33–2.66), and 1.74 (95% CI 1.21–2.52). The HRs for kidney cancer were 1.39 (95% CI 0.85–2.28), and 1.78 (95% CI 1.03–3.07). The HRs for lymphoid and haematopoietic tissue cancer were 1.29 (95% CI 0.90–1.86), and 1.25 (95% CI 0.85–1.84), and for non-Hodgkin's lymphoma 1.96 (95% CI 1.09–3.55), and 2.01 (95% CI 1.05–3.84).

The HRs for all diseases of the respiratory system were 1.04 (95% CI 0.80–1.35), and 1.08 (95% CI 0.82–1.42), and for influenza 3.77 (95% CI 1.58–8.99), and 3.36 (95% CI 1.32–8.58). The HRs for

Table I. Baseline characteristics in the geothermal heating area and the two reference areas according to census 1981.

	Geothermal heating area N (%)	Warm reference area N (%)	Cold reference area N (%)
Number of people	7511 (100)	44 864 (100)	22 431 (100)
Gender			
Men	3893 (51.8)	23 305 (51.9)	11 929 (53.2)
Woman	3618 (48.2)	21 559 (48.1)	10 502 (46.8)
Age, year			
Mean ± SD	28.30 ± 16.35	28.14 ± 16.30	28.06 ± 16.20
Median, IQR (0.25; 0.75)	26 (15; 40)	25 (15; 40)	25 (15; 39)
Education			
Basic education	1829 (24.3)	12 370 (27.6)	6565 (29.3)
Medium education	2088 (27.8)	11 754 (26.2)	5665 (25.3)
Academic education	622 (8.3)	3171 (7.1)	1428 (6.4)
Unclassified	2878 (38.3)	17 061 (38.0)	8481 (37.7)
Missing	94 (1.3)	508 (1.1)	292 (1.3)
Housing			
Single family home	5730 (76.3)	29 236 (65.2)	17 343 (77.3)
Other type of house	1781 (23.7)	15 628 (34.8)	5088 (22.7)
Region			
Urban regions ≥ 500 individuals	5793 (77.1)	30 554 (68.1)	12 839 (57.2)
Rural regions < 500 individuals	1718 (22.9)	14 310 (31.9)	9592 (42.8)

IQR, interquartile range; SD, standard deviation.

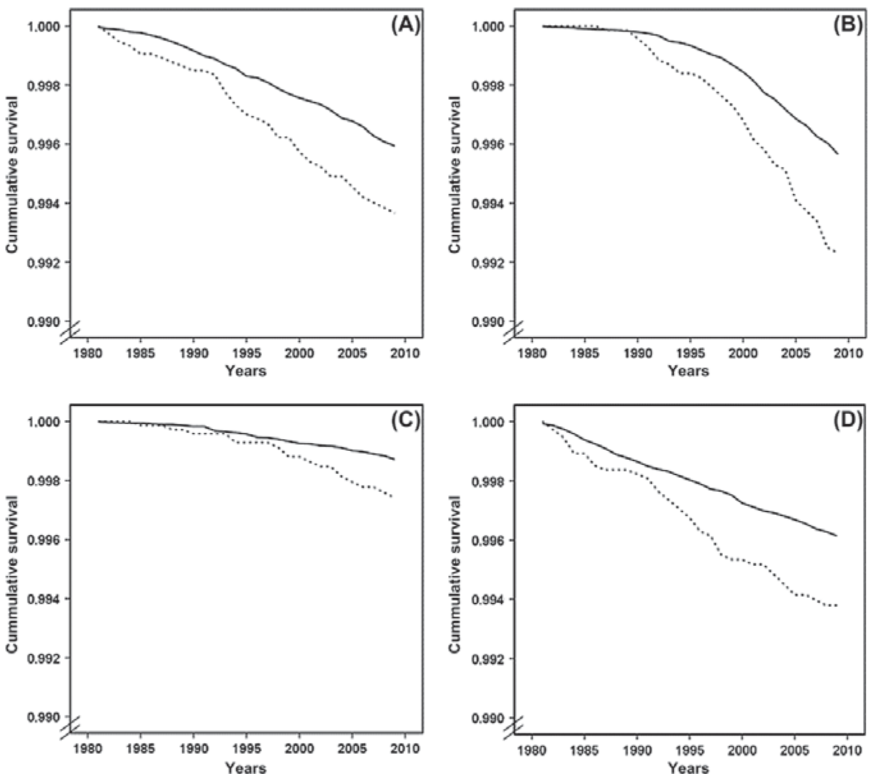

Figure 3. Kaplan-Meier estimates of event-free proportion for death since the census 1981, dashed line indicate population in geothermal water area, and black line population in the combined reference areas, (A) breast cancer death (Log-rank test: $p = 0.006$), (B) prostate cancer death (Log-rank test: $p < 0.000$), (C) non-Hodgkin's lymphoma death (Log-rank test: $p = 0.011$), and (D) suicide (Log-rank test: $p = 0.004$).

suicide and intentional self-harm were 1.72 (95% CI 1.20–2.48), and 1.49 (95% CI 1.03–2.17).

Among men, 596 deaths occurred in the geothermal heating area, and the HR for all causes of death was 1.00 (95% CI 0.91–1.08), adjusted for age, education, housing, and smoking in comparison with the combined reference areas (Table II). The HRs for all cancers were 1.06 (95% CI 0.91–1.23), for prostate cancer 1.88 (95% CI 1.37–2.60), and for non-Hodgkin's lymphoma 2.31 (95% CI 1.21–4.41). The HR for influenza was 3.10 (95% CI 1.09–8.84). The HR for suicide and intentional self-harm was 1.46 (95% CI 1.00–2.13).

Among women, 400 deaths occurred in the geothermal heating area, and the HR for all causes of death was 1.00 (95% CI 0.90–1.11), adjusted for age, education, housing, and smoking in comparison with the combined reference areas (Table II). The HRs for all cancers were 1.04 (95% CI 0.89–1.23), and for breast cancers 1.49 (95% CI 1.06–2.09). The HR for immunoproliferative diseases was 8.39 (95% CI 1.15–61.42) based on two death cases. The HR for influenza was 3.99 (95% CI 1.21–13.18). The HR for suicide and intentional self-harm was 2.05 (95% CI 1.02–4.15).

Restricting the analysis to those 20 years of age and older at the time of the census, there were 949 deaths in the geothermal heating area. In this older part of the cohort, comparison of the geothermal heating area with the combined reference areas gives similar HRs as in the total exposed cohort and HR for all causes of death was 0.99 (95% CI 0.93–1.06). The HRs for all cancers were 1.05 (95% CI 0.93–1.17), for breast cancer 1.40 (95% CI 0.99–2.00), for prostate cancer 1.88 (95% CI 1.36–2.59), for kidney cancer 1.57 (95% 0.98–2.51). The HRs for lymphoid and haematopoietic tissue cancer were 1.33 (95% CI 0.94–1.89), and for non-Hodgkin's lymphoma 2.01 (95% CI 1.16–3.49). The HRs for all diseases of the respiratory system were 1.05 (95% CI 0.82–1.35), and for influenza 3.22 (95% CI 1.48–7.02). The HRs for all external causes were 1.09 (95% CI 0.83–1.75), and suicide and intentional self-harm 1.80 (95% CI 1.21–2.68), adjusted for age, gender, education, type of housing, and smoking habits. HRs for other causes of death did not significantly deviate from unity.

Restricting the analysis to those under 20 years of age at the time of the census, there were 47 deaths in the geothermal heating area. The HRs for all causes of death, all cancer deaths, and suicide and intentional self-harm were higher in the geothermal heating area compared to the combined reference areas, but not to a statistically significant degree. The

Table II. Number of all causes of death and selected causes of death among men and women separately in the geothermal heating area, hazard ratio (HR), 95% confidence intervals (CI) according to comparison with the reference areas combined, adjusted for age, education, type of housing, and smoking habits. Statistically significant HRs are in bold.

	Geothermal heating area	Cold and warm reference areas combined		
	p-yr 96 294	p-yr 882 022		
Causes of death (ICD-10)	No. of deaths	No. of deaths	HR	95% CI
Men				
All causes (A00–Y98)	596	5536	1.00	0.91–1.08
All Neoplasms (C00–C97 and D45–D47)	193	1687	1.06	0.91–1.23
Prostate (C61)	47	239	**1.88**	**1.37–2.60**
Lymphoid and haematopoietic tissue (C81–C96 and D45–D47)	20	162	1.20	0.75–1.93
Non-Hodgkin's lymphoma (C82–C85)	12	45	**2.31**	**1.21–4.41**
Immunoproliferative diseases (C88)	1	6	1.35	0.16–11.57
Diseases of the respiratory system (J00–J99)	32	344	0.92	0.64–1.32
Influenza (J10–J11)	5	17	**3.10**	**1.09–8.84**
All external causes (V01–Y98)	74	656	1.04	0.82–1.33
Suicide and intentional self-harm (X60–X84)	31	190	**1.46**	**1.00–2.13**
	p-yr 91 896	p-yr 822 346		
Women				
All causes ICD-10	400	3570	1.00	0.90–1.11
All Neoplasms (C00–C97 and D45–D47)	167	1386	1.04	0.89–1.23
Breast (C50)	40	230	**1.49**	**1.06–2.09**
Lymphoid and haematopoietic tissue (C81–C96 and D45–D47)	18	104	1.49	0.89–2.47
Non-Hodgkin's lymphoma (C82–C85)	4	28	1.53	0.52–4.46
Immunoproliferative diseases (C88)	2	2	**8.39**	**1.15–61.42**
Diseases of the respiratory system (J00–J99)	38	289	1.20	0.85–1.70
Influenza (J10–J11)	4	11	**3.99**	**1.21–13.18**
All external causes (V01–Y98)	29	184	1.41	0.95–2.10
Suicide and intentional self-harm (X60–X84)	10	39	**2.05**	**1.02–4.15**

p-yr, person years.

HR for breast cancer deaths in this younger part of the cohort, based on four cases, was significantly elevated 4.65 (95% CI 1.33–16.21).

Analysing the breast cancer mortality with additional adjustment for age at first birth, the HR was 1.44 (95% CI 0.94–2.19), when restricted to those 20 years of age and older the HR was 1.29 (95% CI 0.83–2.02), and for those under 20 years of age the HR was 5.91 (95% CI 1.52–22.90).

Discussion

This population-based study on nearly a thousand deaths in areas supplied with geothermal hot water used for heating, bathing and washing for decades, which shows increased mortality for breast and prostate cancer, and non-Hodgkin's lymphoma, confirms results from similarly designed incidence studies on increased risk for these cancers [17,18]. It is thus unlikely that these previous studies on cancer incidence were skewed by detection bias and overdiagnosis [17,18]. The increased mortality for breast cancer in the present study is consistent with the increased incidence of breast cancer among the population in the Furnas village, located in geothermal area of the volcanic island Sao Miguel, in Azores [14]. There was increased mortality for kidney cancer corresponding to the increased kidney cancer incidence in the previous study [18]. In this mortality study it was possible to adjust for social variables such as education and type of housing, and for estimates of age at first birth (reproductive factor) and smoking habits. Contrary to the previous cancer incidence studies, no clear evidence of exposure-response relation were observed between breast and prostate cancers, or non-Hodgkin's lymphoma and the degree of volcanic/geothermal activity of the reference areas in the present study.

Most of the remaining causes of death were in line with averages, and the HRs for diseases of the nervous and circulatory system were close to unity. An exception was an excess for influenza, based on nine cases, but mortality for other diseases of the respiratory system was not increased. In the Rotorua geothermal area study, an increased standardised mortality ratio was found due to all diseases of the respiratory system, confined to female and particularly Maori female, and concerned the subcategories: pneumonia and influenza combined, and chronic obstructive respiratory diseases [12]. In the Tuscan geothermal area study, there seemed also to be an excess mortality for all diseases of the respiratory system among males, mainly due to an excess of pneumoconiosis [13]. The three- to four-fold increase in mortality for influenza was fairly consistent compared to the two reference areas and among both genders in the present study. The significance of these findings is uncertain; however, in the light of previous studies [17,18] one may speculate whether this is an indication of an immunosupression.

Mortality for all external causes of death was not significantly increased; however, suicides were increased for both males and females. This was not hypothesised and came unexpected, as suicide risk is not mentioned in previous mortality studies from geothermal areas [12,13] and is here without explanation. In this connection it is worth pointing out that the proportion of individual living in rural regions was lowest in the geothermal heating area, thus not indicating an overrepresentation of farmers in that population, compared to the reference populations. Further, possible social differences were adjusted for with two variables form the census, educational level and type of housing.

Strength

Strength of the study is the long follow-up time of the cohort. Furthermore, the use of the comprehensive population registries and the personal identification number, which enabled easy and accurate record linkage, strengthen the study. Thus, vital and emigration status were ascertained through the National Registry and the National Cause-of-Death Registry for all individuals in the exposed cohort and the two reference populations. No information was missing from death certificates, and only 0.2% of the causes of death among the exposed cohort were reported on the death certificates as due to unknown and unspecified causes. This low proportion is indicative of the quality of the information.

All death certificates are issued by a physician, and if the deceased person's physician is not able to attest the cause of death or when the circumstances of the death are unexplained, unusual, suspicious, due to intoxication, or following an accident, the death is reported to the police and the medical examiner, who carry out an autopsy and forensic investigations before the death certificate is issued [33]. An in-depth study on the quality of the recording of the cause of death on death certificates in Iceland is not available. However, when evaluating death registration at a global level, the quality of registration data from Iceland was categorised as high overall and ranked in the same category as data from 23 developed countries including the US and the UK [34].

As said previously, the results of this study oppose the possibility of detection bias concerning breast cancer and prostate cancer. Mammography screening has been offered to the female population, aged 49–69 years, since 1987, and the participation rate since then has been around 70%, with no indication of geographical disproportional distribution [27]. No systematic screening for prostate cancer has been carried out in the study populations; however, sporadic prostate-specific antigen testing might have occurred in these populations as elsewhere. In the general population in Iceland the incidence of breast and prostate cancer has been steadily increasing from 1959 to 2010, while mortality for breast cancer has decreased and mortality for prostate cancer has been constant over the period 1995–2010 [27].

Limitation

More than 50 calculations of HR for all causes of death and selected causes of death were performed in the present study. The HRs for the rare causes of death are shown for descriptive purposes; however, the main interest was in relation to cancers, which had been in excess in previous incidence studies [17,18]. The many calculations performed in the study may give rise to concern; however, it has been argued that no adjustment is needed for these [35].

A limitation here is the lack of exact information on the physical and chemical content of the geothermal water used for space heating system since 1972 in the target communities. The components of gas emissions have been documented in other geothermal areas [3,4,6,7]; however, the content of the geothermal hot water has not been investigated for the purpose of this study.

Information of occupation from the census was not available for this study; however, the results were adjusted for social variables, such as education, and type of housing.

Future studies should use length of residency in areas with the geothermal hot water systems as a surrogate for the exposure among these populations. To that information, one should link measurements on physical, chemical and biological components of the geothermal water [36]. In the present study adjustment was made for the levels of individual exposure in terms of social-related variables, and also for smoking habits and reproductive factors on the community level, and these factors do not seem to be associated with cancer mortality. Moreover, the focus should be on factors of concern in previous studies in volcanic areas. A recent study showed evidence of DNA damage among individuals from the volcanically active area in Furnas, Azores [37]. This finding was attributed to degassing in the volcanic environment in general, and particular to the Rn emission [37]. The settings may be different in Iceland; nevertheless the use of geothermal hot water for showering and in spas has analogies with studies on the release of Rn and its decay products from shower water, which leads to transient increase in airborne Rn concentration [38,39]. The decreased lung cancer mortality in the present study, although is not statistically significant, does not indicate serious indoor Rn exposure of the population with the long-term usage of geothermal water.

Conclusion

The significant excess mortality risk of breast and prostate cancers, and non-Hodgkin's lymphoma confirmed the results of similarly designed studies on cancer incidence among populations from high-temperature geothermal areas and users of geothermal hot water. The cancer risk is thus not confined to cancers with good prognosis, but also concerns fatal cancers. Adjustment was made for individual social-related variables, as well as for reproductive factors and smoking habits on the community level. Further studies are needed on the chemical and physical content of the environmental emissions in geothermal areas, and the exposure and the dermal contamination resulting from the use of the geothermal water.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Table I (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.923113).

Supplementary material for Kristbjornsdottir A. and Rafnsson V. Cancer mortality and other causes of death in users of geothermal hot water. Acta Oncol 2015;54:115–23.

Supplementary Table I. Number of all causes of death and selected causes of death among men and women combined in the geothermal heating area, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits. Statistically significant HRs are in bold.

	Geothermal heating area	Warm reference area			Cold reference area		
	p-yr 188 190	p-yr 1 136 686			p-yr 567 682		
Causes of death (ICD-10)	No. of deaths	No. of deaths	HR	95% CI	No. of deaths	HR	95% CI
All causes (A00–Y98)	996	6038	1.01	0.94–1.08	3068	0.98	0.91–1.05
Infectious and parasitic diseases (A00–B99)	4	48	0.51	0.18–1.45	25	0.46	0.16–1.34
All neoplasms (C00–C97 and D45–D47)	360	2047	1.05	0.94–1.18	1026	1.03	0.92–1.17
Oesophagus (C15)	9	47	1.01	0.49–2.09	23	1.13	0.52–2.45
Stomach (C16)	19	139	0.79	0.48–1.29	79	0.75	0.45–1.24
Colon, rectum, and anus (C18–C21)	35	171	1.20	0.82–1.75	88	1.13	0.76–1.68
Bile and liver (C22–C24)	7	53	0.84	0.37–1.89	31	0.68	0.30–1.56
Pancreas (C25)	26	120	1.37	0.88–2.13	52	1.45	0.91–2.33
Larynx (C32)	2	8	1.50	0.30–7.57	6	1.06	0.21–5.34
Lung and bronchus (C33–C34)	70	458	0.93	0.72–1.21	235	0.88	0.67–1.15
Melanoma (C43)	3	25	0.95	0.27–3.28	14	0.67	0.19–2.37
Breast (C50)	41	159	**1.48**	**1.03–2.12**	75	**1.53**	**1.04–2.24**
Ovary (C56–C57)	11	60	1.01	0.52–1.96	33	0.96	0.48–1.90
Prostate (C61)	47	156	**1.88**	**1.33–2.66**	83	**1.74**	**1.21–2.52**
Kidney (C64–C66)	21	91	1.39	0.85–2.28	35	**1.78**	**1.03–3.07**
Bladder (C67)	4	49	0.48	0.17–1.36	23	0.55	0.19–1.61
Brain and central nervous system (C70–C72, C75.1 and C75.3)	11	86	0.77	0.40–1.48	58	0.58	0.30–1.11
Cancer without specification of site (C80)	6	50	0.75	0.31–1.80	21	0.90	0.36–2.25
Lymphoid and haematopoietic tissue (C81–C96 and D45–D47)	38	173	1.29	0.90–1.86	93	1.25	0.85–1.84
Non-Hodgkin's lymphoma (C82–C85)	16	49	**1.96**	**1.09–3.55**	24	**2.01**	**1.05–3.84**
Immunoproliferative diseases (C88)	3	4	2.92	0.63–13.61	4	2.89	0.60–13.82
Multiple Myeloma (C90)	11	46	1.38	0.70–2.73	24	1.34	0.65–2.76
Leukaemia (C91–C95 and D45–D47)	7	68	0.60	0.27–1.34	37	0.59	0.26–1.32
Non-CLL (C91–C95 and D45–D47, except C91.1)	7	57	0.71	0.32–1.59	31	0.69	0.30–1.57
Endocrine, nutritional and metabolic diseases (E00–E90)	10	99	0.58	0.30–1.13	65	**0.47**	**0.24–0.93**
Mental and behavioural disorders (F00–F99)	12	88	0.83	0.45–1.55	33	1.12	0.58–2.18
Diseases of the nervous system and the sense organs (G00–H95)	46	282	0.98	0.71–1.36	130	1.05	0.75–1.47
Diseases of the circulatory system (I00–I99)	346	2195	0.99	0.88–1.11	1118	0.94	0.83–1.06
Ischaemic heart diseases (I20–I25)	213	1284	1.06	0.91–1.23	690	0.94	0.81–1.10
Acute coronary heart disease (I21–I24)	134	812	1.07	0.89–1.30	457	0.89	0.73–1.08
Other heart diseases (I30–I33, I39–I52)	36	190	1.16	0.80–1.69	115	0.94	0.64–1.37
Cerebrovascular diseases (I60–I69)	62	467	0.82	0.62–1.08	207	0.93	0.70–1.24
Diseases of the respiratory system (J00–J99)	70	426	1.04	0.80–1.35	207	1.08	0.82–1.42
Influenza (J10–J11)	9	19	**3.77**	**1.58–8.99**	9	**3.36**	**1.32–8.58**
Pneumonia (J12–J18)	21	134	1.07	0.67–1.73	52	1.32	0.79–2.20
Chronic lower respiratory diseases (J40–J47)	37	237	0.92	0.64–1.31	142	0.94	0.65–1.36
Asthma (J45–J46)	4	16	1.21	0.40–3.72	7	2.31	0.65–8.21
Diseases of the digestive system (K00–K93)	20	154	0.73	0.45–1.18	58	1.07	0.65–1.79
Diseases of the musculoskeletal system/connective tissue (M00–M99)	5	23	1.66	0.60–4.59	12	1.24	0.43–3.58
Diseases of the genitourinary system (N00–N99)	10	77	0.80	0.41–1.58	44	0.69	0.35–1.37
Congenital malformations and chromosomal abnormalities (Q00–Q99)	2	25	0.54	0.12–2.35	9	0.70	0.15–3.22
Symptoms, signs, abnormal findings, ill-defined causes (R00–R99)	5	22	1.49	0.54–4.10	23	0.63	0.24–1.67
Unknown and unspecified causes (R96–R99)	2	20	0.73	0.17–3.27	17	0.34	0.08–1.47
All external causes (V01–Y98)	103	535	1.20	0.96–1.49	305	1.05	0.84–1.31
Accidents (V01–X59)	55	356	0.96	0.71–1.29	202	0.85	0.63–1.14
Transport accidents (V01–V99)	27	190	0.86	0.57–1.30	110	0.78	0.51–1.20
Accidental falls (W00–W19)	9	61	0.90	0.44–1.85	23	1.09	0.50–2.36
Accidental poisoning (X40–X49)	5	31	0.97	0.37–2.57	14	1.05	0.38–2.93
Suicide and intentional self-harm (X60–X84)	41	143	**1.72**	**1.20–2.48**	86	**1.49**	**1.03–2.17**
Events of undetermined intent (Y10–Y34)	4	20	1.59	0.51–4.91	11	1.37	0.41–4.55

p-yr, person years.

Paper IV

PLOS ONE

RESEARCH ARTICLE

Association of Cancer Incidence and Duration of Residence in Geothermal Heating Area in Iceland: An Extended Follow-Up

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Data Availability Statement: The data are both ethically and legally restricted. In these approvals these authorities permitted several record linkages where personal identification numbers of individuals were used, and the registers involved, all named in the manuscript are: the Icelandic Census from 1981, the National Register, the National Roasters, the National Cause-of-Death Register, and the Icelandic Cancer Registry. Requests for access to the data may be sent to The National Bioethics Committee (vsn@vsn.is), Data Protection Commission (postur@personuvernd.is), Statistics Iceland

Abstract

Background

Residents of geothermal areas have higher incidence of non-Hodgkin's lymphoma, breast cancer, prostate cancer, and kidney cancers than others. These populations are exposed to chronic low-level ground gas emissions and various pollutants from geothermal water. The aim was to assess whether habitation in geothermal areas and utilisation of geothermal water is associated with risk of cancer according to duration of residence.

Methods

The cohort obtained from the census 1981 was followed to the end of 2013. Personal identifier was used in record linkage with nation-wide emigration, death, and cancer registries. The exposed population, defined by community codes, was located on young bedrock and had utilised geothermal water supply systems since 1972. Two reference populations were located by community codes on older bedrock or had not utilised geothermal water supply systems for as long a period as had the exposed population. Adjusted hazard ratio (HR), 95% confidence intervals (CI) non-stratified and stratified on cumulative years of residence were estimated in Cox-model.

Results

The HR for all cancer was 1.21 (95% CI 1.12–1.30) as compared with the first reference area. The HR for pancreatic cancer was 1.93 (1.22–3.06), breast cancer, 1.48 (1.23–1.80), prostate cancer 1.47 (1.22–1.77), kidney cancer 1.46 (1.03–2.05), lymphoid and haematopoietic tissue 1.54 (1.21–1.97), non-Hodgkin´s lymphoma 2.08 (1.38–3.15) and basal cell carcinoma of the skin 1.62 (1.35–1.94). Positive dose-response relationship was observed between incidence of cancers and duration of residence, and between incidence of cancer and degree of geothermal/volcanic activity in the comparison areas.

(information@statice.is), and the Icelandic Cancer Registry (skra@krabb.is).

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Competing Interests: The authors have declared that no competing interests exist.

Conclusions

The higher cancer incidence in geothermal areas than in reference areas is consistent with previous findings. As the dose-response relationships were positive between incidence of cancers and duration of residence, it is now more urgent than before to investigate the chemical and physical content of the geothermal water and of the ambient air of the areas to detect recognized or new carcinogens.

Introduction

Environmental pollution and its impact on human health have been considered a serious problem in active volcanic areas and millions of people globally live within those areas [1, 2].

During eruption and post-eruptive phases, volcanoes release numerous hazardous contaminants, including toxic gases and heavy metals [3]. People living in the close vicinity of the volcano are usually those who suffer most in cases of eruption [4]; and people living on volcanic ground may experience long-term exposure to various toxic ground gas emissions, carbon dioxide (CO_2), hydrogen sulphide (H_2S), radon (Rn), sulphur dioxide (SO_2), sulphuric acid (H_2SO_4), hydrogen chloride (HCl), and hydrogen fluoride (HF), which are considered to pose chronic health hazards [5–7]. Several other low-dose exposures have been mentioned, among them arsenic (As), lead (Pb), and mercury (Hg) [3, 8]. The same chemical components are emitted from geothermal fields and fumaroles in Iceland, namely CO_2, H_2S, SO_2 and hydrogen (H_2), and trace elements such as As (1–2 ppb), Hg (0.05 ppb), and Rn (3–100 Bq/l) [9–11] have been identified in the geothermal water.

Long-term studies on populations living on geothermal fields or in volcanic areas are scant and cancer incidence among these populations has so far been the subject of only limited study with inconsistent results [8, 12–14], with the exception of the Icelandic studies and a study from Sicily that show similar results [15–17]. In the study from Rotorua, New Zealand, Bates et al. found an increased risk of nasal and lung cancer among residents in a geothermal field, who were exposed to H_2S [13]. The study from the Azores, Portugal, found an association of female breast cancer and residence on an actively degassing geothermal field, and the authors suggested that trace elements and high Rn exposure might play a role [8]. In a study from Sicily, residents of the volcanic region of Catania province have higher incidence of thyroid cancer than other populations and it is mentioned that the environmental concentration of Rn is elevated in the area; however, it was not possible to conclude on the role of the Rn in this context [14]. In a new study from Sicily, Russo et al. [17] found an increased risk of thyroid cancer and lymphatic leukaemia in men and women; Hodgkin's lymphoma, stomach and breast cancer were higher among women and prostate cancer among men. The authors conclude that increased risk of all cancers and for several tissue-specific types of cancer was a likely consequence of non-anthropogenic environmental pollution, and different cancer-specific carcinogens and mechanisms may be responsible for the higher incidence of certain tumour types among residents in the volcanic area [17]. In two Icelandic studies [15, 16] a higher risk of non-Hodgkin's lymphoma (NHL), breast cancer, prostate cancer, and basal cell carcinoma (BCC) of the skin were found. The same pattern emerged in both these studies. The authors advocated the measurement and detection of possible carcinogens in the gas emissions in the geothermal areas and in the geothermal water used for space heating, washing and bathing [15, 16].

The aim of the study is to assess whether cumulative length of residence in a geothermal heating area, where the inhabitants are exposed through use of the geothermal water for space heating, washing, and bathing, and through the ground gas emissions of geothermal fields in their vicinity, is associated with the risk of cancer.

Methods

Iceland is located in the middle of the North Atlantic Ocean on the Mid-Atlantic Ridge where the North American and Eurasian tectonic plates are moving apart. These movements can be observed in Iceland, and they are related to the volcanic activities in the country. Through the centuries, volcanic eruptions in Iceland have periodically emitted ash and gases, which have been carried downwind to mainland Europe. Historically, such events have been associated with climate change and increased mortality in England and elsewhere [18].

This is a population-based observational study and the source of data was the 1981 National Census in Iceland. The four-digit community codes in the census (Table A in S1 File) were used to define the exposed population as inhabitants of communities that have used geothermal heating supply systems since 1972 or earlier, according to description of all hot water supply systems in Iceland, and the National Registry [11, 19]. In these communities, geothermal water has been used for domestic and greenhouse heating, laundry, bathing, showering, and washing, in spas and swimming pools; however, geothermal water has not been used as drinking water. The geothermal water comes from drilled boreholes that can be up to several hundred meters deep. The water temperature at source ranges from 70°C to 120°C [11]. The geothermal supply distribution systems consist of a network of pipes conducting the water from the boreholes to serve each of the homes and other buildings in the respective community, with few exceptions; the main feeding pipe for the communities can be up to 20 km long. The communities in geothermal heating areas were all located in the central region of the country where the bedrock is less than 3.3 million years old, and some of these communities were on or near even younger bedrock, less than 0.8 million years old. The two reference populations were also identified by the community codes in the census [19]; they had not utilised geothermal heating systems as old as 1972 [11], and age of the bedrock was also taken into consideration [20]. The first of these two reference populations, called the cold reference area, included residents of communities located in the west and east parts of Iceland where the bedrock is more than 3.3 million years old and up to 15 million years old. These communities are well outside the volcanic zone in the central region of the country. The population of the cold reference area is considered the main comparison population in the study. The second reference population, in the area referred to as the warm reference area, included residents of communities located in the central region of the country, where the age of the bedrock is variable but ranging from very young (less than 0.8 million years to 15 million years old). The populations in the area of the capital, Reykjavik, and the adjacent Reykjanes area were not included in the study in order to avoid bias due to capital effect [21]. To summarise: with respect to the age of the bedrock there is a volcanic/geothermal gradient through the areas, lowest in the cold area, middling in the warm area, and highest in the geothermal heating area, with reference to geological studies [22,23], and in that area the communities had had geothermal water supply systems since 1972 or earlier [11]. With the passage of time, it is becoming increasingly difficult to obtain populations in Iceland unexposed to geothermal water, as approximately 90% of all houses and swimming pools are at present heated with geothermal water and 12% of the electricity is generated from geothermal power plants [11]. The exposed area and reference areas were the same as used in the previous mortality study [20].

The characteristics of the populations have been described in previous studies [15, 16, 20]. Briefly, eligible participants were people aged 5–64 years. The census included information on personal identification number, gender, age, residence, education, and type of housing, and these two last mentioned variable are the indicators of the socioeconomic status. Personal identification numbers were used in record linkage with the National Registry to obtain information on possible out-migration and with the National Cause-of-Death Registry to obtain information on vital status and, where applicable, the date of death according to death certificates. These registries are kept at Statistics Iceland. By out-migration, we mean those who have moved abroad, not to be confused with those who have moved domestically from one community to another (see later discussion on place, and length of residence in the study areas). After a person has moved abroad, an eventual cancer diagnosis is not necessarily registered in the Cancer Registry, and due to that uncertainty, that person's follow-up has to be censored at the day of out-migration.

The cancer cases in the study populations were identified by record linkage of the personal identification number with the Cancer Registry (a nation-wide registry of all cancer cases with virtually complete coverage and over 95% of the diagnoses histologically verified) [24]. Thus from the Cancer Registry we obtained information on the cancer site, morphology, and year of diagnosis. BCC has been registered in a special file at the Cancer Registry; it is not counted with the overall cancers, and is analysed separately.

Information on smoking was not collected in the census and thus not available on an individual level. Since 1985, the Public Health Institute of Iceland has collected results from annual surveys on smoking habits among random samples of the population according to gender and postal codes [25]. The estimation of smoking habits on community and gender level was done according to the same procedure as has been described in previous studies [16, 20].

Information on reproductive factors was not available from the census. The reproductive factor, age at first birth, was estimated according to information from Statistics Iceland [19], and in the same manner as in previous studies [16, 20].

Statistics Iceland publishes annually the National Roster of the population with personal identification numbers, addresses and community codes. The information on the duration of residence was obtained from the available National Rosters from the years 1985, 1990, 1995, 2000 and 2004. If the location of an individual was in the same community in the census as in the National Rosters (1985, 1990 . . ..2004), it was assumed that the person had been resident in that community for the number of years between the census and the record of that person in the respective roster. In cases where the individual was not located in the same community in the roster 1985 as in the census 1981, the cumulative number of years of residence was estimated to be less than 5 years. In cases where the individual was located in the same community in the roster 1985 as in census 1981 but not in the same community in the roster 1990 (and so on through the rosters), the cumulative number of years of residence was estimated to be 5 years. The last residence category was estimated to have cumulative years of residence of 24 years or more. There were thus six categories of cumulative residence: less than 5 years, 5 years, 10 years, 15 years, 20 years, and 24 years or more, for the exposed and the reference populations.

Follow-up time started at the day of census, 31 January, 1981, and continued to the date of out-migration, or the date of death, or the date of first diagnosed cancer, or 31 December 2013 (the end of the follow-up period), whichever occurred first. Immortal person-time was taken into consideration, and excluded, which means that from follow-up time allocated to a specific exposure category, we excluded time during which the exposure-category definition was being met, according to Rothman and Greenland [26].

Regardless of exposure categories, survival for the event-free proportion was shown for the geothermal heating area and the cold reference area by Kaplan-Meier estimates for all cancers, breast cancer, prostate cancer, pancreatic cancer and NHL [27].

The plots of the log(-log(survival)) versus log(time) curves were created for exposed group/warm reference group and for exposed group/cold reference group to observe whether resulting in parallel curves or not. By the introduction of an interaction term of the covariate with time the proportional hazard assumption was checked by testing for significance.

The Cox proportional hazard model was used to estimate hazard ratio (HR) and 95% confidence intervals (95% CI) for all cancers and selected cancer site [28]. Covariates were age, gender, educational level, type of housing, smoking habits, and reproductive factors.

The exposed population living in the geothermal heating area was compared with the other populations (warm reference area and cold reference area) in separate analyses. Several calculations were done in the model: crude comparison without any adjustments, comparison with adjustment for age and gender only, and with adjustment for age, gender, educational level, housing, and smoking habits. These calculations had nearly identical results. Then we did analyses with stratification on categories of cumulative years of residence, and then in a separate analysis where five-year latency was applied. Only the results with all adjustment without and with stratification on cumulative years of residence and without and with five-year latency are presented here; however detailed results are shown in Appendix. Separate analyses were done after dividing the material by gender and by splitting the material by four strata on categories of cumulative years of residence and by different age strata, without and with five-year latency.

Due to concerns that variation in prevalence of mutation in the BRCA2 gene across the three study populations might account for our results, we used the method of Axelson and Steenland [29] to evaluate the possible confounding due to this unmeasured genetic factor. Axelson and Steenland introduced their method for evaluating potential confounding effect of smoking in occupational studies, however, the method has been widely used, for example to evaluate confounding due to reproductive factors for the risk of female breast cancer [30]. Mutation in the BRCA2 gene has been studied in families with high risk of breast cancer in both female and male in Iceland [31], and this mutation was detected in 0.6% of the population (based on a random sample), in 7.7% of female breast cancer cases, and in 40% of males with breast cancer. The total 38 cases of males with breast cancer in the census 1981 (N = 184 114, followed from 1981 to 2013), were used to calculated the prevalence of those with and without the mutation in the BRCA2 gene in the three study populations, based on the number of male breast cancer patients, three in the geothermal heating area (n = 7 511), nine in the warm (n = 44 864), and five in the cold (n = 22 431) reference areas. For the mutation in the BRCA2 gene, we assumed that the mutation was the only reason the population in the geothermal heating area had an elevated risk of breast cancer among females. We estimated the geothermal population expected female breast cancer incidence rate [29] using the prevalence in the groups with and without the mutation, and known female breast cancer relative risk comparing those with and without the mutation. These risks were obtained from Thorlacius et al. [32] (modified to take age into account): the risk of breast cancer in a population of BRCA2 carriers as 7, relative to that of a population free from BRCA2 mutation set as 1. This rate was compared with the expected female breast cancer incidence rate in the populations in the warm and cold reference areas, which had been estimated using analogous fractions, and corresponding female breast cancer risk of these populations.

The statistical analyses were performed using the PASW (SPSS) software version 22.

The National Bioethics Committee (VSNb2010060005/03.1) and the Data Protection Commission (2010060524ÞPJ/—) approved the study.

Results

The national census in 1981 included 184,114 individuals or 99.2% of the population aged between 5 and 64 years according to the National Registry [19]. At the end of the follow up on 31 January 2013, 58.4% of individuals in the 1981 census were still alive, had not out-migrated, and were without cancer. Over the studied period, 10.9% of the populations had died, 17.6% had out-migrated, and 13.1% had been diagnosed with first cancer. A total of 24,136 persons were diagnosed with first cancer during the 33 years of the follow up.

The baseline characteristics in the three study populations: geothermal heating area, the warm, and the cold reference areas, are shown in Table 1, and Table B in S1 File.

Fig 1 shows the result of the Kaplan-Meier estimates illustrating the time until any first cancer reported to the Cancer Registry in the geothermal heating area and the cold reference area. A greater proportion of the inhabitants of geothermal heating area were diagnosed with cancer than among the inhabitants of the cold reference area at each time point, and the curves never crossed during the study period.

Fig 2 shows results of the Kaplan-Meier estimates illustrating the time until first occurrence of breast cancer, prostate cancer, NHL, and pancreatic cancer in the geothermal heating area and in the cold reference area.

Table 1. Baseline characteristics in the geothermal heating area and the two reference areas, categories of cumulative years of residence in the respective areas, number of individual, and age at census.

	Geothermal heating area	Warm reference area	Cold reference area
	N (%)	N (%)	N (%)
Number of people	7511 (100)	44 864 (100)	22 431 (100)
Age in years			
Mean ± SD	28.81 ± 16.35	28.65 ± 16.30	28.56 ± 16.20
Median, IQR (0.25; 0.75)	26 (15; 41)	26 (15; 40)	26 (15; 40)
Numbers in categories of cumulative years of residence			
< 5 years	1479 (19.7)	6935 (15.5)	4029 (18.0)
≥ 5 to <10 years	1061 (14.1)	5808 (12.9)	3213 (14.3)
≥ 10 to < 15 years	843 (11.2)	5688 (12.7)	2853 (12.7)
≥ 15 to < 20 years	671 (8.9)	3829 (8.5)	1880 (8.4)
≥ 20 to < 24 years	492 (6.6)	3235 (7.2)	1861 (8.3)
≥ 24 years	2965 (39.5)	19 369 (43.2)	8595 (38.3)
Age (years) at census in categories of cumulative years of residence			
< 5 years			
Mean ± SD	26.83 ± 14.78	26.71 ± 14.93	26.16 ± 14.54
Median, IQR (0.25; 0.75)	23 (17; 34)	24 (17; 34)	24 (16; 33)
≥ 5 to <10 years			
Mean ± SD	24.67 ± 15.86	25.09 ± 15.66	25.39 ± 15.77
Median, IQR (0.25; 0.75)	19 (14; 33)	20 (14; 34)	20 (14; 33)
≥ 10 to < 15 years			
Mean ± SD	25.48 ± 17.09	26.92 ± 17.25	27.02 ± 17.56
Median, IQR (0.25; 0.75)	18 (12; 36)	20 (13; 39)	20 (13; 40)
≥ 15 to < 20 years			
Mean ± SD	27.93 ± 20.24	27.88 ± 19.86	26.96 ± 19.20
Median, IQR (0.25; 0.75)	19 (9; 48)	22 (9; 47)	21 (10; 44)
≥ 20 to < 24 years			
Mean ± SD	31.75 ± 18.79	31.07 ± 19.14	30.24 ± 18.28
Median, IQR (0.25; 0.75)	32 (13; 49)	30 (12; 49)	28 (13; 46)
≥ 24 years			
Mean ± SD	31.95 ± 14.88	30.66 ± 14.97	31.38 ± 14.86
Median, IQR (0.25; 0.75)	31 (20; 43)	30 (19; 42)	30 (20; 42)

Abbreviations: SD standard deviation, IQR inter-quartile range.

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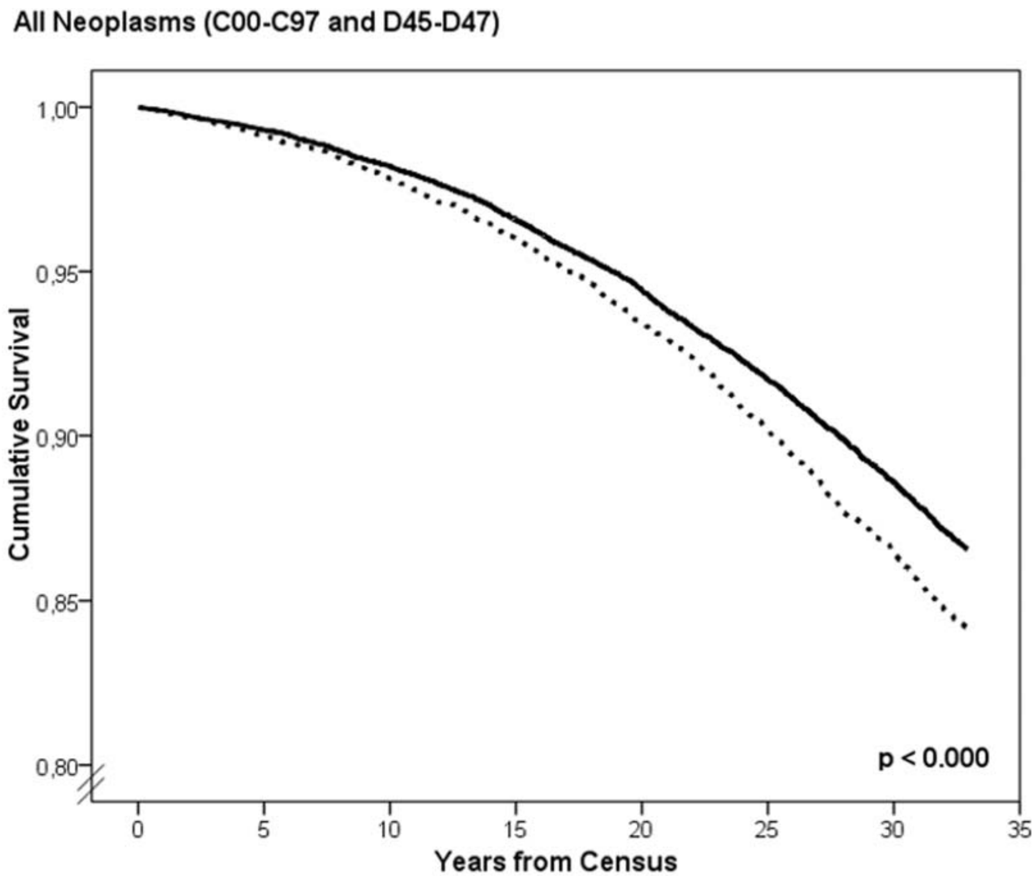

Cold area	**22 431**	**21 717**	**20 493**	**19 216**	**17 781**	**15 067**	**14 186**
Geothermal heating area	**7 511**	**7 233**	**6 803**	**6 323**	**5 790**	**4 892**	**4 578**

Fig 1. Kaplan-Meier estimates of event free proportion for all cancers since the census 1981, dashed line indicate population in geothermal heating area, and black line population in the cold reference area.

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The plots of the log(-log(survival)) versus log(time) curves did not cross and were reasonably parallel, shown in S1 and S2 Figs. The proportional hazard assumption for the Cox model (exposed group/warm reference group) was held (p = 0.76), and same for the other model (exposed group/cold reference group) (p = 0.61), so the Cox regression model were considered appropriate.

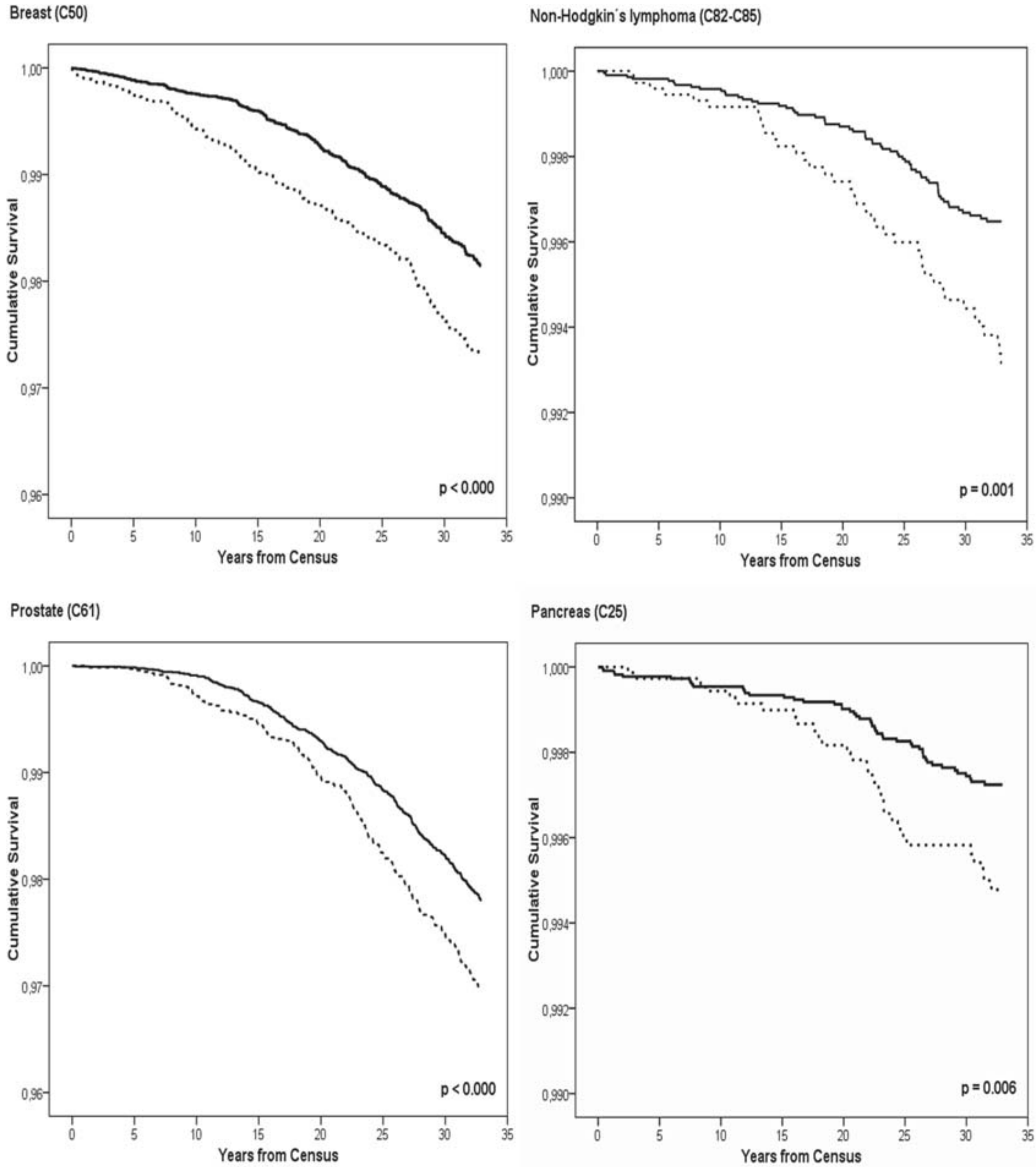

Fig 2. Kaplan-Meier estimates of event free proportion for breast cancer, prostate cancer, pancreas cancer and non-Hodgkin's lymphoma (NHL) since the census 1981. Dashed line indicates population in geothermal heating area, and black line population in the cold reference area.

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Table 2 shows the number of all cancers, and selected cancer sites among the combined genders in the study populations, and the HR and 95% CI adjusted for age, gender, education, type of housing, and smoking habits, both without and with stratification into categories of cumulative residence.

For completeness, all cancer sites with any cancer case in the geothermal heating area are shown in Table C in S1 File, and sites with no case are not shown. The HRs were generally higher in comparison with the cold reference area than with the warm reference area, and were higher when stratified on categories of cumulative years of residence than without such stratification; this was valid in comparison with the cold and warm reference areas. The HRs were higher for all cancers and several of the selected cancer sites, including cancers of pancreas, breast, prostate, and kidney, and the combined cancers of the lymphoid and haematopoietic tissue, counting NHL, and myelodysplastic syndromes (MDS) (Table 2). In the analyses, the HRs for lung cancer were, 0.91 to 0.96, in comparison with the warm and cold reference areas respectively, and the 95% CI included unity. The HRs for BCC were also higher, and showed a similar pattern as for other selected cancer sites shown in Table 2, namely the HRs were higher in comparison with the cold than with the warm reference areas, and the HRs were higher when stratified on categories of cumulative years of residence than without such stratification; this was valid in comparison with the two reference areas.

Table 3 shows the number of all cancers, and selected cancer sites in the study populations when applying five-year latency time. The HR and 95% CI were analysed without and with stratification on cumulative residence, and adjusted for age, gender, education, type of housing, and smoking habits.

All cancer sites with any cancer case in the geothermal heating area are shown in Tables D, E, and F in S1 File, for completeness, and sites with no case are not shown. As in the analyses without latency there was a similar pattern in Table 3 as in previous Table 2, i.e. the HRs were generally higher in comparison with the cold reference area than with the warm reference area, and were higher when stratified on cumulative residence than without such stratification; this was valid in comparison with the cold and warm reference areas. The HRs for all cancer, pancreatic cancer, and the combined cancers of the lymphoid and haematopoietic tissue, including NHL, and MDS, were higher in these analyses with five-year latency time than without applying the latency. On the contrary, the HRs for breast, prostate, and kidney cancers were high, albeit not as high as in the analyses without latency time, and the accompanying 95% CI included unity. The HRs for BCC were increased when applying five-year latency time; however they were lower than in the analyses without latency time, and only in comparison with the cold reference area did the 95% CI not include unity.

When analysing men separately, 517 cancers had occurred in the geothermal heating area, and the HR for all cancers was 1.07 (95% CI 0.97–1.18) in the comparison with the warm reference area, and 1.21 (95%CI 1.09–1.34) in comparison with the cold reference area, with stratification on cumulative years of residence, and adjusted for age, education, housing, and smoking habits (Table G in S1 File). The HRs for the different cancer sites showed a similar pattern as in the analyses of the genders combined. In Table G in S1 File, all cancer sites with any case among men in the geothermal heating area are shown for completeness.

In the analysis of women separately, 471 cancers had occurred in the geothermal heating area, and the HR for all cancers was 1.14 (95% CI 1.03–1.26) in the comparison with the warm reference area, and 1.21 (95% CI 1.09–1.35) in comparison with the cold reference area, with stratification on cumulative years of residence, and adjusted for age, education, housing, and smoking habits (Table H in S1 File). The HRs for the different cancer sites showed a similar pattern as in the analyses of the genders combined. In Table H in S1 File, all cancer sites with any case among women in the geothermal heating area are shown for completeness.

Table 2. Number of all cancers and selected cancer sites among men and women combined, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of cancers	No of cancers	Not stratified		Stratified		No of cancers	Not stratified		Stratified	
Cancers (ICD-10)			HR	95%CI	HR	95%CI		HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	988	5331	1.06	0.99–1.14	**1.10****	**1.02–1.18**	2524	**1.17*****	**1.09–1.26**	**1.21*****	**1.12–1.30**
Pancreas (C25)	30	126	1.50	0.99–2.27	**1.53***	**1.00–2.32**	49	**1.87****	**1.18–2.95**	**1.93****	**1.22–3.06**
Lung and bronchus (C33-C34)	92	578	0.91	0.72–1.14	0.94	0.75–1.18	300	0.92	0.73–1.17	0.96	0.76–1.22
Breast (C50)	161	740	**1.23***	**1.03–1.46**	**1.27****	**1.07–1.52**	326	**1.42*****	**1.18–1.72**	**1.48*****	**1.23–1.80**
Prostate (C61)	172	803	**1.27****	**1.07–1.51**	**1.32*****	**1.11–1.57**	377	**1.43*****	**1.19–1.72**	**1.47*****	**1.22–1.77**
Kidney (C64-C66)	49	241	1.21	0.88–1.67	1.27	0.92–1.75	103	**1.40**	**1.00–1.97**	**1.46***	**1.03–2.05**
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	97	419	**1.30***	**1.03–1.64**	**1.36****	**1.08–1.72**	199	**1.49*****	**1.17–1.91**	**1.54*****	**1.21–1.97**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	39	137	**1.78*****	**1.22–2.59**	**1.90*****	**1.30–2.77**	62	**2.00*****	**1.33–3.03**	**2.08*****	**1.38–3.15**
NHL, peripheral T-cells (C84)	6	14	**2.85***	**1.02–7.99** [b]	**2.91***	**1.04–8.19** [b]	5	**3.84***	**1.11–13.31** [b]	**3.93***	**1.12–13.74** [a]
NHL, unspecified (C85)	9	11	**5.13*****	**1.99–13.21** [a]	**5.23*****	**2.02–13.54** [a]	4	**6.81*****	**2.03–22.80** [a]	**6.75*****	**2.01–22.64** [a]
Leukaemia (C91-C95, D45-D47)	30	145	1.10	0.73–1.65	1.13	0.75–1.70	71	1.30	0.85–2.00	1.37	0.89–2.11
Chronic lymphocytic leukaemia (CLL)(C91.1)	10	45	1.16	0.57–2.35	1.22	0.59–2.49	24	1.30	0.62–2.73	1.45	0.68–3.08
Non-CLL (C91-C95, D45-D47, except C91.1)	20	100	1.07	0.65–1.76	1.09	0.67–1.80	47	1.31	0.77–2.22	1.35	0.80–2.29
Myelodysplastic syndromes (MDS) (D46)	8	18	2.31	0.95–5.58	**2.44***	**1.01–5.90** [b]	6	**4.02***	**1.38–11.71** [a]	**4.07***	**1.39–11.93** [a]
MDS, unspecified (D46.9)	8	12	**3.41***	**1.32–8.83** [a]	**3.70****	**1.42–9.64** [a]	3	**8.20*****	**2.10–32.10** [a]	**8.09*****	**2.06–31.79** [a]
Other LH, uncertain (D47)	3	14	1.24	0.34–4.54	1.41	0.38–5.21	7	1.21	0.31–4.70	1.14	0.29–4.44
Other LH thrombocythemia (D47.3)	3	2	**11.43***	**1.64–79.80** [b]	**12.72***	**1.80–89.74** [b]	1	8.61	0.85–86.98	7.53	0.74–76.48
Not included in all cancers											
Basal cell carcinoma of skin (C44)	177	781	**1.22***	**1.03–1.45**	**1.28*****	**1.08–1.52**	335	**1.54*****	**1.28–1.85**	**1.62*****	**1.35–1.94**

Statistically significant HRs are bolded.

[a] 95%CI computed with bootstrap method did not include unity.

[b] 95%CI computed with bootstrap method included unity.

* $p < 0.05$

** $p < 0.01$

*** $p < 0.005$.

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Table 3. Number of all cancers and selected cancer sites among men and women combined, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of cancers	No of cancers	Not stratified		Stratified		No of cancers	Not stratified		Stratified	
Cancers (ICD-10)			HR	95%CI	HR	95%CI		HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	372	1845	1.11	0.99–1.25	**1.16***	**1.03–1.30**	959	**1.19*****	**1.06–1.35**	**1.22*****	**1.08–1.37**
Pancreas (C25)	11	36	1.92	0.94–3.91	**2.11***	**1.03–4.34**	19	1.90	0.90–4.00	2.01	0.95–4.25
Lung and bronchus (C33-C34)	40	209	1.01	0.71–4.42	1.03	0.72–1.46	126	0.99	0.69–1.41	1.01	0.71–1.45
Breast (C50)	56	277	1.11	0.82–1.49	1.14	0.85–1.54	133	1.28	0.94–1.75	1.29	0.94–1.76
Prostate (C61)	57	288	1.15	0.85–1.54	1.21	0.90–1.63	138	1.31	0.96–1.79	1.35	0.98–1.85
Kidney (C64-C66)	16	90	1.03	0.59–1.78	1.06	0.61–1.84	41	1.17	0.66–2.09	1.18	0.66–2.10
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	37	143	**1.49***	**1.02–2.17**	**1.61***	**1.10–2.36**	72	**1.64***	**1.10–2.44**	**1.70***	**1.14–2.55**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	17	49	**2.12***	**1.18–3.80**	**2.30****	**1.27–4.14**	20	**2.98*****	**1.50–5.89**	**3.02*****	**1.52–6.00**
NHL, peripheral T-cells (C84)	4	5	**4.22***	**1.02–17.44** [b]	**4.24***	**1.02–17.64** [b]	2	**8.77***	**1.27–60.56** [a]	**8.93***	**1.25–63.69** [a]
NHL, unspecified (C85)	3	0					1	**12.38***	**1.12–137.23** [b]	10.23	0.96–108.93
Leukaemia (C91-C95, D45-D47)	10	50	1.08	0.53–2.18	1.22	0.60–2.49	28	1.11	0.54–2.28	1.25	0.60–2.59
Chronic lymphocytic leukaemia (CLL)(C91.1)	1	15	0.35	0.05–2.71	0.41	0.05–3.21	8	0.40	0.06–2.87	0.59	0.07–4.93
Non-CLL (C91-C95, D45-D47, except C91.1)	9	35	1.40	0.65–3.01	1.58	0.73–3.42	20	1.40	0.64–3.09	1.48	0.67–3.26
Myelodysplastic syndromes (MDS) (D46)	7	10	**3.97***	**1.40–11.29** [a]	**4.17****	**1.46–11.94** [a]	2	**11.30*****	**2.25–56.67** [a]	**11.46*****	**2.27–57.80** [a]
MDS, unspecified (D46.9)	7	6	**6.48*****	**2.01–20.93** [a]	**7.18*****	**2.19–23.52** [a]	1	**20.59****	**2.51–169.15** [a]	**20.74****	**2.50–171.80** [a]
Other LH, uncertain (D47)	1	1	6.34	0.34–118.41	8.68	0.44–170.13	0				
Other LH thrombocythemia (D47.3)	1	1	6.34	0.34–118.41	8.68	0.44–170.13	0				
Not included in all cancers											
Basal cell carcinoma of skin (C44)	74	357	1.06	0.82–1.37	1.11	0.86–1.44	154	**1.44***	**1.09–1.91**	**1.48****	**1.12–1.96**

Statistically significant HRs are bolded.

[a] 95%CI computed with bootstrap method did not include unity.

[b] 95%CI computed with bootstrap method included unity.

* $p < 0.05$

** $p < 0.01$

*** $p < 0.005$.

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In a comparison between the study areas, when we split the material according to four categories of cumulative years of residence in the respective areas analysing the cancer risk in these strata separately, and adjusting for age, gender, education, housing, and smoking habits, the HRs were higher in the four strata, and these results are shown in detail in Tables I, and J in S1 File.

Restricting the analyses into different groups according to age in the census, we divided the population into those under 20 years of age, under 25 years, and so on in incremental 5-year age groups, up to under 40 years of age, and into 40 years of age or older. The comparison with the cold and warm reference areas without and with stratification on categories of cumulative years of residence yield a similar pattern as in Tables 2 and 3 (detailed results are shown in Tables K, L, and M in S1 File); and the results were similar when applying five-year latency time, shown in Table N in S1 File.

Analysing breast cancer risk with additional adjustment for age at first birth, the HRs in the geothermal heating area in comparison with the warm reference area were 1.17 (95% CI 0.94–1.46), and 1.19 (95% CI 0.96–1.48), without and with stratification on cumulative residence, respectively. The HRs in comparison with cold reference area were 1.37 (1.08–1.74), and 1.43 (1.13–1.82), without and with stratification, respectively. When applying five-year latency time, the HRs in comparison with the warm reference area were 1.07 (0.74–1.54), and 1.12 (0.78–1.61), without and with stratification on cumulative residence respectively; and in comparison with the cold reference area, the HRs were 1.17 (0.79–1.74), and 1.18 (0.79–1.76), without and with stratification, respectively.

Using the relative risk from the study of Thorlacius et al. [32], and the estimated prevalence's of those with and without the mutation of the BRCA2 gene the risks of female breast cancer were calculated, and are shown in Table O in S1 File. In the population of the geothermal heating area we obtained the value of (7*1.16 + 1*98.84) = 106.96, and for the population of the warm reference area the value was (7*0.58 + 1*99.42) = 103.48, and for the population of the cold reference area the value was (7*0.65 + 1*99.35) = 103.90. The predictive value [29] for the comparison of geothermal heating area versus warm reference area was (106.96/103.48) = 1.03, or 3% increase. The corresponding predictive value for comparison of geothermal heating area versus cold reference area was (106.96/103.90) = 1.03, also 3% increase.

Discussion

This population-based cohort study with 33 years follow-up with nearly a thousand cancer cases in the geothermal heating area, where geothermal water was used for heating, bathing and washing for decades, showed statistically significant higher risk for all cancers, pancreatic cancer, breast cancer, prostate cancer, kidney cancer, combined cancers of the lymphoid and haematopoietic tissue, NHL, MDS, and BCC of the skin than in the reference areas. The risk for these cancer sites was higher in comparison with the cold reference area than with the warm reference area, through the degree of volcanic/geothermal activity, indicating a dose-response association. When taking cumulative years of residence in the areas into consideration, the risk for these cancer sites were generally higher compared with the risk when length of residence was not accounted for, again in a dose-response manner. In the present study, it was possible to adjust for age, gender, social variables such as education and type of housing, on an individual basis, and for estimates of age at first birth and smoking habits on the community level.

The result of this study with extended follow-up confirms the results from previous similarly designed incidence studies on higher risk for all cancers, pancreatic cancer, breast cancer, prostate cancer, kidney cancer, lymphoid and haematopoietic tissue cancers, NHL, and BCC of the skin [15, 16]. The higher incidence for all cancers and breast cancer in the present study is consistent with the higher incidence of all cancers and breast cancer among the population in the geothermal area than in the non-geothermal area of Furnas, Azores [8], and is also consistent with results of a recently published study indicating higher incidence for all cancers, breast cancer and prostate cancer among the population in Catania, the area with highest volcanic activity compared with the areas with less volcanic activity in Sicily, Italy [17].

A study from Furnas, Azores showed evidence of DNA damage in residents of volcanic active areas in comparison with an area without manifestations of volcanic activity [33].

Recently it has been discussed [34, 35] that disproportional distribution of the mutation of the BRCA2 gene in the geothermal population as compared to the reference populations in previous studies [15, 16] may be a confounding factor, in particular for the association with breast cancer among women [34, 35]. However, this mutation only occurs in 0.6% of the Icelandic population [31] and therefore is not likely to account for our results. Nevertheless, we used the Axelson and Steenland method [29] to estimate the influence of this factor on our findings revealing that although the estimated mutation prevalence is higher in geothermal areas, this increase only account for 3% of the total female breast cancer incidence. Thus, our findings contrasting breast cancer in geothermal areas to warm or cold reference areas yielding HR of 1.27 and 1.48 respectively, are unlikely to be explained solely by confounding due to this mutation. Also, BRCA2 mutation carriers have well documented increased risk of ovarian cancer [36] and the decreased risk of ovarian cancer in geothermal areas in our study further argues against confounding effects of mutation in the BRCA2 gene.

The long follow-up and the number of cancer cases found in the geothermal heating area enabled us to break these into rare subcategories of cancer sites, and it is of interest to observe the details of the 97 cases of combined cancer of the lymphoid and haematopoietic tissue. Several categories of lymphomas and leukaemias had higher HRs, and the 95% CI for all NHL, peripheral T-cell NHL (ICD-10 code C84), and unspecified NHL (ICD-10 code C85) did not include unity. NHL comprises heterogeneous malignancies with regard to clinical, etiological and histological entity [37]. Viral infections, immune deficiencies, and high dose ionizing radiation have been associated with NHL [37], and recent studies support the indications that farming, hairdressing, and textile occupations, red meat and processed meat consumption, and autoimmune conditions may be related to NHL risk [38–40]. The HRs for MDS, based on eight cases, were higher in all analyses, and the 95% CI did not include unity. The cases of MDS were not secondary to cancer treatment, as the study is confined to first cancers only, and these cases were not classified as therapy-related, but had the location code D46.9, MDS, unspecified. All cancers in the ICD-10 category D had morphology behavioural code /3 indicating malignant neoplasm. In another study, familial aggregation was not found in patients with MDS [41], and MDS may arise secondarily after chemotherapy and radiotherapy [42], or exposure to ionizing radiation and benzene [43,44], thus well-known environmental carcinogens.

The causes are unknown for the higher HRs of many cancer sites in the present study, which are related to length of cumulative residence in the study areas. In reflection on this, it is difficult to explain the risk for the different cancer sites by a single component of the ground gas emission in the geothermal area, or traces of chemicals in the geothermal water. When considering the classification of human carcinogens according to the International Agency for Research on Cancer [45], two carcinogens in particular i.e. As and Rn come to mind, as these have been mentioned in previous studies on cancer risk among populations in geothermal areas. A recent mortality study in an old volcanic area provided evidence of association of low dose (below 10 ppb) As in drinking water and cancer risk [46], and in a case-control study a positive association between BCC and a low dose exposure to As was found [47]. The concentrations of As in geothermal well water used for bathing in the geothermal heating area range from 11 to 116 ppb [48], and should be contrasted to < 0.3 ppb in water used for bathing in the cold reference area [49, 50]. According to a recent nation-wide survey of indoor Rn concentration in Iceland, a mean of 13 Bq/m^3 is among the lowest in the world [51]. Nevertheless the amount of Rn in the geothermal water in the geothermal heating area (9 Bq/l) (used for bathing) [10] is approximately four times the amount of Rn in water used for bathing in the cold reference area (approximately 1.5 Bq/l) [49, 50]. The role of these differences in concentrations is unknown; bearing in mind that dermal exposure may in this situation be of greater importance than exposure through inhalation or ingestion.

Recently, naturally occurring radioactive material (NORM) has been discovered above exemption limit for the first time in Iceland, located in scale precipitated in pipes close to wells (boreholes) in one of the geothermal power plants [52]. The NORM is from the U-238 decay chain and exceeded the exemption limit 10 Bq/g ten to twenty times [52]. At present, more measurements are planned to be undertaken in different power plants. Whether these findings have significance for utilization of the geothermal water in settings other than the power plants, i.e. in dwellings, is still uncertain, as is the possibly far-fetched association with the increased cancer incidence found among the population of the geothermal heating areas in the present study.

Strength

We count to the strength of the study the long follow-up time of the cohort. Furthermore, the use of the comprehensive population registries and the personal identification number, which enabled easy and accurate record linkage, strengthen the study. Thus, duration of residence, vital, and out-migration status were ascertained through the National Rosters, the National Registry, and the National Cause-of-Death Registry for all individuals in the exposed cohort and the two reference populations, i.e. in the same way for everybody in the study. Information on the outcome, the cancer incidence, was obtained by similarly performed record linkage of every individual of the exposed and the non-exposed populations with the Cancer Registry. 95% of the cancer cases reported to the Cancer Registry are histologically verified, and in the case of BCC, all diagnoses are histologically confirmed.

Screening for breast cancer with mammography has been offered nation-wide to all women 40–69 years of age since 1987, and there are no indications of regional differences in the participation rate [24]. Systematic screening for prostate cancer or skin cancer have not been implemented or recommended in Iceland.

To our best knowledge, the present study is the first to report on cumulative years of residence for every individual in the geothermal heating area (the exposed population) and in the two reference populations, and thus it enables us to take the length of residence, as a surrogate of the exposure to volcanic/geothermal environment, and the use of geothermal water, into consideration in the risk assessments.

Limitation

Numerous calculations of HRs for all cancer and selected cancer sites were performed in the present study. The HRs for the rare sites of cancers are shown for descriptive purposes. The many calculations performed in the study may give rise to concern regarding multiple comparisons; however, it has been argued that no adjustment is needed for these [53].

The study is limited by the lack of individual exposure information with regard to mode and magnitude of ground gas emission in the geothermal area and the reference areas, and the detailed information on the components of the drinking water, and the geothermal water.

However we were able to take length of residence in the areas into consideration as a surrogate of exposure.

The possibility of unknown confounding cannot be excluded, however in the multivariate analysis we were able to adjust for socioeconomic status (level of education, and type of housing), age, and gender on individual level, and smoking habits and age at first birth on community level.

Access to the health care system was found to be easier and the use of the health care system was found to be more frequent, concerning cardiovascular diseases, outside than inside the capital area in Iceland in a recent doctoral thesis [54], however we are not aware of differences in these aspects between the study populations.

In the course of time, geothermal water has become more widely used in Iceland hindering identification of population without the exposure in question. One way to address this problem in future study is to select appropriate reference population from counties without the exposure, in order to increase further the comparability.

In future studies, the data on cumulative years of residence in the respective areas should be used to estimate the long-term exposure to different physical and chemical components occurring in dermal contact with water, in the environment, and in the indoor air, based on historical data, or currently measured concentrations with regard to known carcinogenic factors or mechanisms.

Conclusion

The significant high cancer risk is consistent with previous findings in the geothermal area and users of geothermal water. Positive dose-response manner of relationship between incidence of cancers and cumulative years of residence, and gradient of geothermal/volcanic activity were shown and need further consideration. Adjustment was made for individual social-related variables, as well as for reproductive factors and smoking habits on the community level. Further studies are needed on the chemical and physical content of the environmental emissions in geothermal areas, and the exposure and the dermal contamination resulting from the use of geothermal water.

Supporting Information

S1 Fig. The log(-log(survival)) versus log(time) curves for exposed group (dashed line) and warm reference group (black line).
(TIF)

S2 Fig. The log(-log(survival)) versus log(time) curves for exposed group (dashed line) and cold reference group (black line).
(TIF)

S1 File. Table A. Codes and names of communities in the study populations according to National Registry in 1981. Table B. Baseline characteristics of the study populations, data source were Census 1981[a], Public Health Institute of Iceland[b], Statistics Iceland[c] and National Roasters[d]. Table C. Number of all cancers and cancer sites with any case among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas. Table D. Number of all cancers and cancer sites with any case among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas. Table E. Number of all cancers and cancer sites with any case among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas. Table F. Number of all cancers and select cancer sites any case among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas. Table G. Number of all cancers and cancer sites with any case among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits without and with stratification into categories of cumulative years of residence in the respective areas. Table H. Number of all cancers and cancer sites with any case among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits without and with stratification into categories of cumulative years of residence in the respective areas. Table I. Number of all cancers, and selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, split in four categories of cumulative years of residence in the respective areas. Table J. Number of all cancers, and selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, split in four categories of cumulative years of residence in the respective areas. Table K. Number of all cancers, and selected cancer sites among men and women combined, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas. Table L. Number of all cancers, and selected cancer sites among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas. Table M. Number of selected cancer sites among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas. Table N. Number of selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted

on different age categories in the respective areas. Table O. Number of individuals, number of male breast cancer cases, number of individuals with and without mutation of the BRCA2 gene, the prevalence of those with, and without the mutation according to Thorlacius et al. [29], and predictive values for breast cancer among females according to the method of Axelson and Steenland [27], and using the relative risk for breast cancer among female according to Thorlacius et al. [30], in the geothermal area in comparison with warm and cold reference areas, and the combined capital area and Reykjanes.
(DOC)

Author Contributions

Conceived and designed the experiments: AK TA VR. Performed the experiments: AK TA VR. Analyzed the data: AK TA VR. Wrote the paper: AK TA VR.

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Table A. Codes and names of communities in the study populations according to National Registry in 1981.

Geothermal heating area

6100	Husavik [2]	8100	Selfoss [2]	8711	Biskupstungnahreppur [3]
6607	Skutustadahreppur [3]	8708	Skeidahreppur [3]	8712	Laugardalshreppur [3]
6610	Reykjahreppur [3]	8710	Hrunamannahreppur[3]	8716	Hveragerdishreppur [2]

Cold reference area

3712	Skogarstrandarhreppur [3]	4805	Reykjafjardarhreppur [3]	7501	Skeggjastadahreppur [3]
3801	Hordudalshreppur [3]	4806	Nauteyrarhreppur [3]	7502	Vopnafjardarhreppur [2]
3802	Middalshreppur [3]	4807	Snaefjallahreppur [3]	7503	Hlidarhreppur [3]
3803	Haukadalshreppur [3]	4901	Arneshreppur [3]	7504	Jokuldalshreppur [3]
3804	Laxardalshreppur [3]	4902	Kaldrananeshreppur [3]	7505	Fljotsdalshreppur [3]
3805	Hvammshreppur [3]	4903	Hrofbergshreppur [3]	7506	Fellahreppur [3]
3806	Fellsstrandarhreppur [3]	4904	Holmavikurhreppur [3]	7604	Eidahreppur [3]
3807	Klofningshreppur [3]	4905	Kirkjubolshreppur [3]	7605	Mjoafjardarhreppur [3]
3808	Skardshreppur [3]	4906	Fellahreppur [3]	7606	Nordfjardarhreppur [3]
3809	Saurbaejarhreppur [3]	4907	Ospakseyrarhreppur [3]	7607	Helgustadahreppur [3]
4000	Isafjordur [2]	4908	Baejarhreppur [3]	7609	Reydarfjardarhreppur [2]
4100	Bolungarvik [2]	5501	Stadarhreppur [3]	7610	Faskrudsfjardarhreppur [3]
4501	Geiradalshreppur [3]	5502	Fremri-Torfustadahreppur[3]	7611	Budahreppur [2]
4502	Reykholahreppur [3]	5503	Ytri-Torfustadahreppur [3]	7612	Stodvarhreppur [3]
4503	Gufudalshreppur [3]	5504	Hvammstangahreppur [3]	7613	Breiddalshreppur [3]
4504	Mulahreppur [3]	5505	Kirkjuhvammshreppur [3]	7614	Beruneshreppur [3]
4505	Flateyjarhreppur [3]	5506	Thverarhreppur [3]	7615	Bulandshreppur [3]
4601	Bardastrandarhreppur [3]	5507	Thorkelsholahreppur [3]	7616	Geithellnahreppur [3]
4602	Raudasandshreppur [3]	5601	Ashreppur [3]	7701	Baejarhreppur [3]
4603	Patrekshreppur [2]	5602	Sveinsstadahreppur [3]	7702	Nesjahreppur [3]
4604	Talknafjardarhreppur [3]	5603	Torfalaekjarhreppur [3]	7703	Hafnarhreppur [2]
4605	Ketildalshreppur [3]	5604	Blonduoshreppur [2]	7704	Myrahreppur [3]
4606	Sudurfjardahreppur [3]	5605	Svinavatnshreppur [3]	7705	Borgarhafnarhreppur [3]
4701	Audkuluhreppur [3]	5606	Bolstadahlidarhreppur [3]	7706	Hofshreppur [3]
4702	Thingeyjarhreppur [3]	5607	Engihlidarhreppur [3]	7507	Tunguhreppur [3]
4703	Myrahreppur [3]	5608	Vindhaelishreppur [3]	7508	Hjaltastadarhreppur [3]
4704	Mosfellshreppur [3]	5609	Hofdahreppur [2]	7509	Borgarfjardarhreppur [3]
4705	Flateyrarhreppur [3]	5610	Skagahreppur [3]	7511	Seydisfjardarhreppur [3]
4706	Sudureyrarhreppur [3]	7000	Seydisfjordur [2]	7601	Skriddalshreppur [3]
4803	Sudavikurhreppur [3]	7100	Neskaupstadur [2]	7602	Vallahreppur [3]
4804	Ogurhreppur [3]	7200	Eskifjordur [2]	7603	Egilsstadahreppur [2]

Warm reference area

2603	Kjalarnes [3]	5704	Seiluhreppur [3]	6704	Prestholahreppur [3]
2604	Kjosarhreppur [3]	5705	Lytingsstadahreppur [3]	6705	Raufarhafnarhreppur [3]
3000	Akranes [2]	5706	Akrahreppur [3]	6706	Svalbardshreppur [3]
3501	Strandarhreppur [3]	5707	Ripurhreppur [3]	6707	Thorshafnarhreppur [3]
3502	Skilmannahreppur [3]	5708	Vidvikurhreppur [3]	6708	Saudaneshreppur [3]
3503	Innri-Akraneshreppur [3]	5709	Holahreppur [3]	8000	Vestmannaeyjar [2]
3504	Leirar- og Melahreppur [3]	5710	Hofshreppur [3]	8501	Horgslandshreppur [3]
3505	Andakilshreppur [3]	5711	Hofsoshreppur [3]	8502	Kirkjubaejarhreppur [3]
3506	Skorradalshreppur [3]	5712	Fellshreppur [3]	8503	Skaftartunguhreppur [3]
3507	Lundarreykjadalshreppur [3]	5713	Haganeshreppur [3]	8504	Leidvallarhreppur [3]
3508	Reykholtsdalshreppur [3]	5714	Holtshreppur [3]	8505	Alftavershreppur [3]
3509	Halsahreppur [3]	6000	Akureyri [2]	8506	Hvammshreppur [3]
3601	Hvitarsiduhreppur [3]	6200	Olafsfjordur [2]	8507	Dyrholahreppur [3]
3602	Thverarhlidarhreppur [3]	6300	Dalvik [2]	8601	A-Eyjafjallahreppur [3]
3603	Nordurardalshreppur [3]	6501	Grimseyjarhreppur [3]	8602	V-Eyjafjallahreppur [3]
3604	Stafholtstungnahreppur[3]	6502	Svarfadardalshreppur [3]	8603	A-Landeyjahreppur [3]
3605	Borgarhreppur [3]	6504	Hriseyjarhreppur [3]	8604	V-Landeyjahreppur [3]
3606	Borgarneshreppur [2]	6505	Arskogshreppur [3]	8605	Fljotshlidarhreppur [3]
3607	Alftaneshreppur [3]	6506	Arnarneshreppur [3]	8606	Hvolhreppur [2]
3608	Hraunhreppur [3]	6507	Skriduhreppur [3]	8607	Rangarvallahreppur [2]
3701	Kolbeinsstadahreppur [3]	6508	Oxnadalshreppur [3]	8608	Landmannahreppur [3]
3702	Eyjahreppur [3]	6509	Glaesibaejarhreppur [3]	8609	Holtahreppur [3]
3703	Miklaholtshreppur [3]	6510	Hrafnagilshreppur [3]	8610	Asahreppur [3]
3704	Stadarsveit [3]	6511	Saurbaejarhreppur [3]	8611	Djuparhreppur [3]
3705	Breiduvikurhreppur [3]	6512	Ongulsstadahreppur [3]	8701	Gaulverjabaejarhreppur [3]
3706	Neshreppur [2]	6601	Svalbardsstrandarhreppur [3]	8702	Stokkseyrarhreppur [3]
3707	Olafsvikurhreppur [2]	6602	Grytubakkahreppur [3]	8703	Eyrarbakkahreppur [3]
3708	Frodarhreppur [3]	6604	Halshreppur [3]	8704	Sandvikurhreppur [3]
3709	Eyrarsveit [2]	6605	Ljosavatnshreppur [3]	8706	Hraungerdishreppur [3]
3710	Helgafellssveit [3]	6606	Barddaelahreppur [3]	8707	Villingaholtshreppur [3]
3711	Stykkisholmshreppur [2]	6608	Reykdaelahreppur [3]	8709	Gnupverjahreppur [3]
5000	Siglufjordur [2]	6609	Adaldaelahreppur [3]	8713	Grimsneshreppur [3]
5100	Saudarkrokur [2]	6611	Tjorneshreppur [3]	8714	Thingvallahreppur [3]
5701	Skefilsstadahreppur [3]	6701	Kelduneshreppur [3]	8715	Grafningshreppur [3]
5702	Skardshreppur [3]	6702	Oxarfjardarhreppur [3]	8717	Olfushreppur [2]
5703	Stadarhreppur [3]	6703	Fjallahreppur [3]	8718	Selvogshreppur [3]

Capital area, and south-west peninsula of Reykjanes

0000	Reykjavik [1]	1603	Bessastadahreppur [3]	2502	Hafnarhreppur [3]

1000	Kopavogur [2]	1604	Mosfellshreppur [2]	2503	Midneshreppur [2]
1100	Seltjarnarnes [2]	2200	Keflavik [2]	2504	Gerdahreppur [2]
1300	Gardabaer [2]	2300	Grindavik [2]	2506	Vatnsleysustrandahreppur[3]
1400	Hafnarfjordur [2]	2400	Njardvik [2]		

[1] The capital, n = 65.961, [2] Other urban regions, n ≥ 500 and ≤ 12.195, [3] Rural regions, n < 500.

Table B. Baseline characteristics of the study populations, data source were Census 1981[a], Public Health Institute of Iceland[b], Statistics Iceland[c] and National Roasters[d].

	Geothermal heating area N (%)	Warm reference area N (%)	Cold reference area N (%)
Number of people[a]	7511 (100)	44 864 (100)	22 431 (100)
Gender[a]			
Men	3893 (51.8)	23 305 (51.9)	11 929 (53.2)
Woman	3618 (48.2)	21 559 (48.1)	10 502 (46.8)
Age, year[a]			
Mean ± SD	28.81 ± 16.35	28.65 ± 16.30	28.56 ± 16.20
Median, IQR (0.25 ; 0.75)	26 (15 ; 41)	26 (15 ; 40)	26 (15 ; 40)
Education[a]			
Basic education	1829 (24.3)	12 370 (27.6)	6565 (29.3)
Medium education	2088 (27.8)	11 754 (26.2)	5665 (25.3)
Academic education	622 (8.3)	3171 (7.1)	1428 (6.4)
Unclassified	2878 (38.3)	17 061 (38.0)	8481 (37.7)
Missing	94 (1.3)	508 (1.1)	292 (1.3)
Housing[a]			
Single family home	5730 (76.3)	29 236 (65.2)	17 343 (77.3)
Other type of house	1781 (23.7)	15 628 (34.8)	5088 (22.7)
Region[a]			
Urban regions ≥ 500 individuals	5793 (77.1)	30 554 (68.1)	12 839 (57.2)
Rural regions < 500 individuals	1718 (22.9)	14 310 (31.9)	9592 (42.8)
Never smoker %[b]			
Mean ± SD	43.8 ± 4.7	46.9 ± 5.7	44.7 ± 8.0
Median, IQR (0.25 ; 0.75)	43.3 (40 ; 45)	46.7 (44 ; 50)	46.5 (42 ; 49)
Proportion giving birth before 25 years of age[c]			
Mean ± SD	4.25 ± 2.03	2.18 ± 0.65	2.17 ± 0.78
Median, IQR (0.25 ; 0.75)	3.42 (3.08 ; 6.67)	2.18 (1.73 ; 2.28)	2.48 (1.27 ; 2.84)
Numbers in categories of cumulative years of residence[ad]			
< 5 years	1479 (19.7)	6935 (15.5)	4029 (18.0)
≥ 5 to <10 years	1061 (14.1)	5808 (12.9)	3213 (14.3)
≥ 10 to < 15 years	843 (11.2)	5688 (12.7)	2853 (12.7)
≥ 15 to 20 years	671 (8.9)	3829 (8.5)	1880 (8.4)
≥ 20 to 24 years	492 (6.6)	3235 (7.2)	1861 (8.3)
≥ 24 years	2965 (39.5)	19 369 (43.2)	8595 (38.3)
Age (years) at census in categories of cumulative years of residence[ad]			
< 5 years			
Mean ± SD	26.83 ± 14.78	26.71 ± 14.93	26.16 ± 14.54
Median, IQR (0.25 ; 0.75)	23 (17 ; 34)	24 (17 ; 34)	24 (16 ; 33)
≥ 5 to <10 years			
Mean ± SD	24.67 ± 15.86	25.09 ± 15.66	25.39 ± 15.77

Median, IQR (0.25 ; 0.75)	19 (14 ; 33)	20 (14 ; 34)	20 (14 ; 33)
≥ 10 to < 15 years			
Mean ± SD	25.48 ± 17.09	26.92 ± 17.25	27.02 ± 17.56
Median, IQR (0.25 ; 0.75)	18 (12 ; 36)	20 (13 ; 39)	20 (13 ; 40)
≥ 15 to 20 years			
Mean ± SD	27.93 ± 20.24	27.88 ± 19.86	26.96 ± 19.20
Median, IQR (0.25 ; 0.75)	19 (9 ; 48)	22 (9 ; 47)	21 (10 ; 44)
≥ 20 to 24 years			
Mean ± SD	31.75 ± 18.79	31.07 ± 19.14	30.24 ± 18.28
Median, IQR (0.25 ; 0.75)	32 (13 ; 49)	30 (12 ; 49)	28 (13 ; 46)
≥ 24 years			
Mean ± SD	31.95 ± 14.88	30.66 ± 14.97	31.38 ± 14.86
Median, IQR (0.25 ; 0.75)	31 (20 ; 43)	30 (19 ; 42)	30 (20 ; 42)

Table C. Number of all cancers and cancer sites with any case among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 97 911	p-yr 557 815					p-yr 299 878				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	988	5331	1.06	0.99 to 1.14	**1.10**	**1.02 to 1.18**	2524	**1.17**	**1.09 to 1.26**	**1.21**	**1.12 to 1.30**
Lip, oral cavity, and pharynx (C00-C14)	16	103	0.79	0.46 to 1.36	0.80	0.47 to 1.38	41	1.19	0.67 to 2.14	1.23	0.69 to 2.22
Oesophagus (C15)	13	72	0.95	0.52 to 1.75	0.99	0.54 to 1.83	36	1.12	0.59 to 2.12	1.13	0.59 to 2.14
Stomach (C16)	30	196	0.87	0.58 to 1.28	0.88	0.59 to 1.30	114	0.80	0.53 to 1.19	0.81	0.54 to 1.21
Small intestine (C17)	4	25	0.87	0.30 to 2.59	0.92	0.31 to 2.73	13	1.36	0.43 to 4.37	1.53	0.47 to 4.98
Colon, rectum, and anus (C18-C21)	90	473	1.11	0.88 to 1.41	1.16	0.92 to 1.47	219	1.21	0.95 to 1.55	1.24	0.97 to 1.59
Bile and liver (C22-C24)	10	79	0.71	0.36 to 1.40	0.74	0.37 to 1.45	34	0.90	0.44 to 1.84	0.93	0.45 to 1.90
Pancreas (C25)	30	126	1.50	0.99 to 2.27	**1.53**	**1.00 to 2.32**	49	**1.87**	**1.18 to 2.95**	**1.93**	**1.22 to 3.06**
Nasal cavity and middle ear (C30)	1	9	0.83	0.10 to 7.11	0.83	0.10 to 7.13	5	0.57	0.07 to 4.93	0.61	0.07 to 5.30
Larynx (C32)	4	32	0.76	0.26 to 2.21	0.75	0.25 to 2.19	14	0.90	0.29 to 2.74	0.90	0.29 to 2.76
Lung and bronchus (C33-C34)	92	578	0.91	0.72 to 1.14	0.94	0.75 to 1.18	300	0.92	0.73 to 1.17	0.96	0.76 to 1.22
Bone (C40-C41)	4	21	1.05	0.35 to 3.18	0.98	0.33 to 2.96	6	1.93	0.54 to 6.87	2.00	0.56 to 7.12
Melanoma (C43)	24	138	0.93	0.60 to 1.46	0.99	0.63 to 1.55	57	1.27	0.79 to 2.05	1.32	0.81 to 2.13
Other cancer of skin (C44)	26	184	0.80	0.52 to 1.22	0.83	0.54 to 1.27	88	0.88	0.57 to 1.36	0.89	0.57 to 1.38
Kaposi´s sarcoma (C46)	1	10	0.56	0.07 to 4.68	0.60	0.07 to 5.09	7	0.40	0.05 to 3.30	0.45	0.54 to 3.74
Peritoneum (C48)	2	15	0.61	0.14 to 2.72	0.60	0.14 to 2.69	7	0.89	0.19 to 4.31	0.93	0.19 to 4.53
Soft tissue sarcoma (C49)	6	37	0.91	0.37 to 2.21	0.95	0.39 to 2.31	15	1.18	0.45 to 3.04	1.26	0.48 to 3.26
Breast (C50)	161	740	**1.23**	**1.03 to 1.46**	**1.27**	**1.07 to 1.52**	326	**1.42**	**1.18 to 1.72**	**1.48**	**1.23 to 1.80**
Vulva (C51)	3	9	1.75	0.45 to 6.78	1.69	0.43 to 6.65	5	1.88	0.44 to 7.95	2.17	0.51 to 9.31
Vagina (C52)	1	2	3.08	0.23 to 41.26	3.33	0.24 to 46.49	3	0.91	0.09 to 8.84	1.36	0.13 to 13.87
Cervix uteri (C53)	14	81	0.93	0.52 to 1.67	0.90	0.51 to 1.62	31	1.33	0.71 to 2.51	1.36	0.72 to 2.56
Uterus (C54-C55)	22	115	1.14	0.71 to 1.84	1.22	0.76 to 1.97	59	1.07	0.65 to 1.74	1.12	0.68 to 1.83
Ovary (C56-C57)	20	145	0.83	0.52 to 1.35	0.88	0.54 to 1.43	64	0.91	0.55 to 1.50	0.97	0.58 to 1.60
Penis (C60)	2	11	1.00	0.21 to 4.79	1.11	0.23 to 5.36	3	2.14	0.32 to 14.22	1.90	0.28 to 12.95

Prostate (C61)	172	803	**1.27**	**1.07 to 1.51**	**1.32**	**1.11 to 1.57**	377	**1.43**	**1.19 to 1.72**	**1.47**	**1.22 to 1.77**
Testis (C62)	2	42	0.30	0.07 to 1.25	0.28	0.07 to 1.19	23	0.28	0.07 to 1.17	0.29	0.07 to 1.22
Kidney (C64-C66)	49	241	1.21	0.88 to 1.67	1.27	0.92 to 1.75	103	**1.40**	**1.00 to 1.97**	**1.46**	**1.03 to 2.05**
Bladder (C67)	44	242	0.97	0.70 to 1.35	1.00	0.72 to 1.40	137	0.96	0.69 to 1.36	1.01	0.72 to 1.42
Urinary organs, unspecified (C68)	1	2	2.68	0.21 to 33.75	2.22	0.17 to 29.77	1	3.36	0.20 to 55.46	3.54	0.22 to 57.47
Brain and central nervous system (C70-C72, C75.1 and C75.3)	11	99	0.68	0.36 to 1.29	0.68	0.36 to 1.30	41	0.87	0.44 to 1.71	0.87	0.44 to 1.72
Thyroid gland (C73)	25	131	1.16	0.75 to 1.82	1.21	0.77 to 1.89	68	1.10	0.70 to 1.75	1.16	0.73 to 1.84
Cancer without specification of site (C80)	11	114	0.61	0.32 to 1.14	0.63	0.33 to 1.18	57	0.60	0.31 to 1.14	0.62	0.33 to 1.19
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	97	419	**1.30**	**1.03 to 1.64**	**1.36**	**1.08 to 1.72**	199	**1.49**	**1.17 to 1.91**	**1.54**	**1.21 to 1.97**
Hodgkin´s lymphoma (C81)	6	34	0.89	0.37 to 2.17	0.90	0.37 to 2.21	14	1.50	0.55 to 4.03	1.49	0.55 to 4.02
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	39	137	**1.78**	**1.22 to 2.59**	**1.90**	**1.30 to 2.77**	62	**2.00**	**1.33 to 3.03**	**2.08**	**1.38 to 3.15**
NHL, follicular (C82)	7	30	1.21	0.52 to 2.82	1.34	0.57 to 3.16	13	1.76	0.70 to 4.44	1.80	0.71 to 4.56
NHL, diffuse (C83)	17	82	1.38	0.80 to 2.39	1.48	0.85 to 2.57	40	1.38	0.77 to 2.48	1.45	0.80 to 2.62
NHL, peripheral T-cells (C84)	6	14	**2.85**	**1.02 to 7.99** [b]	**2.91**	**1.04 to 8.19** [b]	5	**3.84**	**1.11 to 13.31** [b]	**3.93**	**1.12 to 13.74** [a]
NHL, unspecified (C85)	9	11	**5.13**	**1.99 to 13.21** [a]	**5.23**	**2.02 to 13.54** [a]	4	**6.81**	**2.03 to 22.80** [a]	**6.75**	**2.01 to 22.64** [a]
Immunoproliferative diseases (C88)	6	25	1.35	0.53 to 3.40	1.51	0.59 to 3.85	12	1.48	0.56 to 3.96	1.68	0.62 to 4.53
Multiple Myeloma (C90)	16	76	1.16	0.66 to 2.02	1.20	0.68 to 2.10	39	1.22	0.68 to 2.18	1.21	0.68 to 2.18
Leukaemia (C91-C95, D45-D47)	30	145	1.10	0.73 to 1.65	1.13	0.75 to 1.70	71	1.30	0.85 to 2.00	1.37	0.89 to 2.11
Non-CLL (C91-C95, D45-D47, except C91.1)	20	100	1.07	0.65 to 1.76	1.09	0.67 to 1.80	47	1.31	0.77 to 2.22	1.35	0.80 to 2.29
Lymphoid leukemia (C91)	12	62	0.98	0.52 to 1.84	1.00	0.53 to 1.90	28	1.35	0.68 to 2.67	1.45	0.72 to 2.89
Acute lymphoid leukemia (C91.0)	1	12	0.49	0.06 to 3.96	0.48	0.06 to 3.84	2	2.34	0.17 to 32.47	2.45	0.17 to 34.95
Chronic lymphocytic leukaemia (CLL)(C91.1)	10	45	1.16	0.57 to 2.35	1.22	0.59 to 2.49	24	1.30	0.62 to 2.73	1.45	0.68 to 3.08
Other lymphoid leukemia (C91.2 to C91.9)	1	5	0.89	0.10 to 7.82	0.90	0.10 to 7.95	2	1.42	0.11 to 17.71	1.12	0.09 to 14.61
Myeloid leukemia (C92)	6	38	0.92	0.38 to 2.22	0.89	0.37 to 2.17	27	0.72	0.30 to 1.75	0.76	0.31 to 1.86
Acute myeloid leukemia (C92.0)	4	26	0.94	0.32 to 2.80	0.94	0.32 to 2.79	20	0.61	0.21 to 1.80	0.63	0.21 to 1.86
Other myeloid leukemia (C92.1 to C92.9)	2	12	0.88	0.19 to 4.04	0.83	0.18 to 3.81	7	1.14	0.23 to 5.57	1.32	0.27 to 6.53
Other and unspecified leukemia (C93 to C95)	1	7	0.65	0.08 to 5.44	0.67	0.08 to 5.70	0				
Myelodysplastic syndromes (MDS)	8	18	2.31	0.95 to 5.58	**2.44**	**1.01 to 5.90** [b]	6	**4.02**	**1.38 to 11.71** [a]	**4.07**	**1.39 to 11.93** [a]

(D46)											
MDS, unspecified (D46.9)	8	12	**3.41**	**1.32 to 8.83** [a]	**3.70**	**1.42 to 9.64** [a]	3	**8.20**	**2.10 to 32.10** [a]	**8.09**	**2.06 to 31.79** [a]
Other LH, uncertain (D47)	3	14	1.24	0.34 to 4.54	1.41	0.38 to 5.21	7	1.21	0.31 to 4.70	1.14	0.29 to 4.44
Other LH thrombocythemia (D47.3)	3	2	**11.43**	**1.64 to 79.80** [b]	**12.72**	**1.80 to 89.74** [b]	1	8.61	0.85 to 86.98	7.53	0.74 to 76.48
Not included in all cancers											
	p-yr 101 014	p-yr 574 065					p-yr 307 763				
Basal cell carcinoma of the skin (BCC) (C44)	177	781	**1.22**	**1.03 to 1.45**	**1.28**	**1.08 to 1.52**	335	**1.54**	**1.28 to 1.85**	**1.62**	**1.35 to 1.94**

Abbreviation: p-yr, person years.

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity.

Table D. Number of all cancers and cancer sites with any case among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 65 169	p-yr 362 298					p-yr 201 705				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	372	1845	1.11	0.99 to 1.25	**1.16**	**1.03 to 1.30**	959	**1.19**	**1.06 to 1.35**	**1.22**	**1.08 to 1.37**
Lip, oral cavity, and pharynx (C00-C14)	3	37	0.40	0.12 to 1.32	0.43	0.13 to 1.40	12	0.90	0.24 to 3.37	0.93	0.25 to 3.52
Oesophagus (C15)	5	35	0.82	0.31 to 2.15	0.84	0.32 to 2.23	16	1.05	0.38 to 2.89	1.09	0.39 to 3.01
Stomach (C16)	9	49	0.96	0.46 to 2.00	1.03	0.49 to 2.14	29	0.98	0.46 to 2.08	1.02	0.48 to 2.16
Small intestine (C17)	1	10	0.58	0.07 to 4.82	0.56	0.07 to 4.62	8	0.63	0.07 to 5.48	0.70	0.08 to 6.16
Colon, rectum, and anus (C18-C21)	32	163	1.09	0.74 to 1.62	1.16	0.78 to 1.72	78	1.27	0.84 to 1.92	1.29	0.85 to 1.96
Bile and liver (C22-C24)	4	22	1.05	0.35 to 3.18	1.14	0.37 to 3.47	7	1.77	0.52 to 6.10	1.82	0.53 to 6.30
Pancreas (C25)	11	36	1.92	0.94 to 3.91	**2.11**	**1.03 to 4.34**	19	1.90	0.90 to 4.00	2.01	0.95 to 4.25
Larynx (C32)	2	9	0.91	0.19 to 4.35	1.00	0.21 to 4.85	7	0.87	0.18 to 4.25	0.84	0.17 to 4.09
Lung and bronchus (C33-C34)	40	209	1.01	0.71 to 1.42	1.03	0.72 to 1.46	126	0.99	0.69 to 1.41	1.01	0.71 to 1.45
Bone (C40-C41)	1	6	0.91	0.10 to 7.97	1.01	0.11 to 8.98	2	1.74	0.15 to 19.58	1.64	0.15 to 18.67
Melanoma (C43)	11	58	0.96	0.50 to 1.87	1.05	0.54 to 2.05	28	1.22	0.60 to 2.45	1.21	0.60 to 2.44
Other cancer of skin (C44)	12	73	0.88	0.47 to 1.65	0.93	0.49 to 1.74	41	0.88	0.46 to 1.68	0.88	0.46 to 1.69
Kaposi´s sarcoma (46)	1	3	1.42	0.14 to 14.63	1.94	0.16 to 23.32	3	0.76	0.07 to 8.17	1.27	0.12 to 13.48
Soft tissue sarcoma (C49)	2	10	0.81	0.18 to 3.75	0.95	0.20 to 4.45	6	1.00	0.20 to 4.98	1.10	0.22 to 5.53
Breast (C50)	56	277	1.11	0.82 to 1.49	1.14	0.85 to 1.54	133	1.28	0.94 to 1.75	1.29	0.94 to 1.76
Vulva (C51)	2	4	2.56	0.45 to 14.57	2.72	0.46 to 16.06	1	7.15	0.63 to 80.94	8.26	0.73 to 94.00
Cervix uteri (C53)	8	21	1.91	0.82 to 4.45	1.92	0.82 to 4.49	14	1.72	0.72 to 4.12	1.68	0.70 to 4.01
Uterus (C54-C55)	10	28	1.99	0.93 to 4.23	2.10	0.98 to 4.50	24	1.28	0.61 to 2.68	1.35	0.64 to 2.85
Ovary (C56-C57)	7	44	1.06	0.46 to 2.41	1.10	0.48 to 2.51	19	1.12	0.47 to 2.66	1.17	0.49 to 2.80
Penis (C60)	2	2	5.90	0.66 to 52.35	6.94	0.78 to 62.10	1	6.19	0.55 to 69.15	5.49	0.47 to 64.31
Prostate (C61)	57	288	1.15	0.85 to 1.54	1.21	0.90 to 1.63	138	1.31	0.96 to 1.79	1.35	0.98 to 1.85
Testis (C62)	2	13	0.94	0.20 to 4.46	0.87	0.18 to 4.15	4	1.62	0.28 to 9.22	1.66	0.29 to 9.49
Kidney (C64-C66)	16	90	1.03	0.59 to 1.78	1.06	0.61 to 1.84	41	1.17	0.66 to 2.09	1.18	0.66 to 2.10

Bladder (C67)	19	91	1.07	0.64 to 1.78	1.11	0.67 to 1.86	55	1.07	0.63 to 1.81	1.13	0.67 to 1.91
Brain and central nervous system (C70-C72, C75.1 and C75.3)	6	27	1.45	0.57 to 3.70	1.45	0.57 to 3.71	11	1.61	0.59 to 4.36	1.56	0.58 to 4.24
Thyroid gland (C73)	11	51	1.19	0.60 to 2.34	1.25	0.63 to 2.47	33	1.00	0.50 to 1.97	1.01	0.51 to 2.01
Cancer without specification of site (C80)	5	26	1.05	0.39 to 2.79	1.05	0.39 to 2.82	14	1.21	0.43 to 3.39	1.21	0.43 to 3.41
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	37	143	**1.49**	**1.02 to 2.17**	**1.61**	**1.10 to 2.36**	72	**1.64**	**1.10 to 2.44**	**1.70**	**1.14 to 2.55**
Hodgkin´s lymphoma (C81)	1	10	0.62	0.08 to 5.07	0.60	0.07 to 4.91	5	0.97	0.10 to 9.21	0.89	0.09 to 8.41
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	17	49	**2.12**	**1.18 to 3.80**	**2.30**	**1.27 to 4.14**	20	**2.98**	**1.50 to 5.89**	**3.02**	**1.52 to 6.00**
NHL, follicular (C82)	1	14	0.35	0.05 to 2.75	0.38	0.05 to 3.01	5	0.86	0.09 to 7.80	0.76	0.08 to 6.82
NHL, diffuse (C83)	9	30	2.04	0.93 to 4.51	**2.27**	**1.02 to 5.05** [b]	12	2.35	0.97 to 5.70	**2.51**	**1.02 to 6.14** [a]
NHL, peripheral T-cells (C84)	4	5	**4.22**	**1.02 to 17.44** [b]	**4.24**	**1.02 to 17.64** [b]	2	**8.77**	**1.27 to 60.56** [a]	**8.93**	**1.25 to 63.69** [a]
NHL, unspecified (C85)	3	0					1	**12.38**	**1.12 to 137.23** [b]	10.23	0.96 to 108.93
Immunoproliferative diseases (C88)	4	9	2.71	0.78 to 9.45	2.95	0.83 to 10.50	7	2.15	0.60 to 7.68	2.47	0.68 to 9.06
Multiple Myeloma (C90)	5	25	1.08	0.40 to 2.90	1.16	0.43 to 3.15	11	1.40	0.49 to 4.05	1.37	0.47 to 3.97
Leukaemia (C91-C95, D45-D47)	10	50	1.08	0.53 to 2.18	1.22	0.60 to 2.49	28	1.11	0.54 to 2.28	1.25	0.60 to 2.59
Non-CLL (C91-C95, D45-D47, except C91.1)	9	35	1.40	0.65 to 3.01	1.58	0.73 to 3.42	20	1.40	0.64 to 3.09	1.48	0.67 to 3.26
Lymphoid leukemia (C91)	1	17	0.30	0.04 to 2.32	0.35	0.05 to 2.68	9	0.37	0.05 to 2.93	0.51	0.06 to 4.20
Chronic lymphocytic leukaemia (CLL)(C91.1)	1	15	0.35	0.05 to 2.71	0.41	0.05 to 3.21	8	0.40	0.06 to 2.87	0.59	0.07 to 4.93
Other and unspecified leukemia (C93 to C95)	1	1	3.22	0.20 to 52.54	6.15	0.35 to 108.18	0				
Myelodysplastic syndromes (MDS) (D46)	7	10	**3.97**	**1.40 to 11.29** [a]	**4.17**	**1.46 to 11.94** [a]	2	**11.30**	**2.25 to 56.67** [a]	**11.46**	**2.27 to 57.80** [a]
MDS, unspecified (D46.9)	7	6	**6.48**	**2.01 to 20.93** [a]	**7.18**	**2.19 to 23.52** [a]	1	**20.59**	**2.51 to 169.15** [a]	**20.74**	**2.50 to 171.80** [a]
Other LH, uncertain (D47)	1	1	6.34	0.34 to 118.41	8.68	0.44 to 170.13	0				
Other LH thrombocythemia (D47.3)	1	1	6.34	0.34 to 118.41	8.68	0.44 to 170.13	0				
Not included in all cancers											
	p-yr 67 151	p-yr 371 689					p-yr 206 015				
Basal cell carcinoma of the skin (BCC) (C44)	74	357	1.06	0.82 to 1.37	1.11	0.86 to 1.44	154	**1.44**	**1.09 to 1.91**	**1.48**	**1.12 to 1.96**

Abbreviation: p-yr, person years.

[a] 95% CI computed with bootstrap method did not include unity. [b] 95% CI computed with bootstrap method included unity.

Table E. Number of all cancers and cancer sites with any case among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 32 035	p-yr 181 102					p-yr 100 523				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	189	984	1.07	0.91 to 1.26	1.13	0.96 to 1.33	478	**1.22**	**1.03 to 1.45**	**1.26**	**1.07 to 1.50**
Lip, oral cavity, and pharynx (C00-C14)	1	21	0.23	0.03 to 1.74	0.25	0.03 to 1.85	10	0.65	0.07 to 6.22	0.68	0.07 to 6.60
Oesophagus (C15)	4	29	0.71	0.24 to 2.10	0.73	0.25 to 2.16	13	1.05	0.34 to 3.24	1.15	0.37 to 3.59
Stomach (C16)	4	31	0.67	0.23 to 1.96	0.68	0.23 to 1.98	22	0.57	0.20 to 1.67	0.60	0.20 to 1.76
Small intestine (C17)	1	8	0.63	0.07 to 5.29	0.61	0.07 to 5.12	5	1.01	0.10 to 10.36	1.15	0.11 to 12.21
Colon, rectum, and anus (C18-C21)	18	96	1.07	0.63 to 1.80	1.14	0.68 to 1.94	46	1.22	0.71 to 2.12	1.26	0.72 to 2.18
Bile and liver (C22-C24)	3	16	1.41	0.38 to 5.20	1.47	0.40 to 5.43	5	2.06	0.46 to 9.30	2.16	0.47 to 9.83
Pancreas (C25)	6	17	2.05	0.76 to 5.54	2.30	0.84 to 6.25	7	2.88	0.95 to 8.73	**3.19**	**1.04 to 9.82**
Larynx (C32)	2	7	1.17	0.23 to 5.93	1.26	0.24 to 6.51	7	0.87	0.18 to 4.25	0.84	0.17 to 4.09
Lung and bronchus (C33-C34)	23	111	1.16	0.72 to 1.85	1.24	0.77 to 1.99	53	1.32	0.81 to 2.16	1.34	0.82 to 2.20
Melanoma (C43)	4	21	1.14	0.37 to 3.50	1.24	0.40 to 3.82	8	1.58	0.47 to 5.34	1.52	0.45 to 5.17
Other cancer of skin (C44)	8	43	1.06	0.48 to 2.33	1.13	0.51 to 2.50	18	1.37	0.59 to 3.16	1.38	0.59 to 3.21
Kaposi´s sarcoma (46)	1	3	1.42	0.14 to 14.63	1.94	0.16 to 23.32	3	0.76	0.07 to 8.17	1.27	0.12 to 13.48
Soft tissue sarcoma (C49)	1	7	0.54	0.07 to 4.41	0.62	0.08 to 5.13	2	1.58	0.14 to 17.62	2.18	0.19 to 25.60
Breast (C50)	1	2	5.17	0.30 to 87.66	4.88	0.28 to 84.61	0				
Penis (C60)	2	2	5.90	0.66 to 52.35	6.94	0.78 to 62.10	1	6.19	0.55 to 69.15	5.49	0.47 to 64.31
Prostate (C61)	57	288	1.15	0.85 to 1.54	1.21	0.90 to 1.63	138	1.31	0.96 to 1.79	1.35	0.98 to 1.85
Testis (C62)	2	13	0.94	0.20 to 4.46	0.87	0.18 to 4.15	4	1.62	0.28 to 9.22	1.66	0.29 to 9.49
Kidney (C64-C66)	9	56	0.91	0.44 to 1.89	0.93	0.45 to 1.94	24	1.10	0.51 to 2.38	1.10	0.51 to 2.38
Bladder (C67)	15	71	1.06	0.59 to 1.89	1.11	0.62 to 1.98	44	1.08	0.60 to 1.96	1.14	0.63 to 2.07
Brain and central nervous system (C70-C72, C75.1 and C75.3)	2	17	0.80	0.17 to 3.69	0.81	0.18 to 3.72	7	0.86	0.18 to 4.16	0.92	0.19 to 4.45
Thyroid gland (C73)	3	13	1.07	0.29 to 3.92	1.10	0.30 to 4.04	7	1.71	0.38 to 7.72	1.67	0.37 to 7.53
Cancer without specification of site	3	10	1.60	0.41 to 6.17	1.60	0.41 to 6.27	9	1.23	0.31 to 4.90	1.21	0.30 to 4.87

(C80)											
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	19	86	1.28	0.76 to 2.16	1.35	0.80 to 2.29	39	1.55	0.89 to 2.70	1.64	0.93 to 2.87
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	10	29	**2.35**	**1.08 to 5.13**	**2.51**	**1.15 to 5.50**	16	1.93	0.86 to 4.33	1.97	0.87 to 4.43
NHL, diffuse (C83)	6	18	2.50	0.91 to 6.85	2.63	0.96 to 7.22	10	1.80	0.65 to 5.00	1.91	0.68 to 5.35
NHL, peripheral T-cells (C84)	3	5	3.55	0.74 to 16.99	3.72	0.77 to 17.89	2	**14.18**	**1.21 to 166.01**	**15.69**	**1.21 to 204.03**
NHL, unspecified (C85)	1	0					1	3.44	0.20 to 58.57	2.90	0.17 to 48.62
Immunoproliferative diseases (C88)	2	3	3.44	0.45 to 26.26	3.19	0.39 to 26.08	3	2.26	0.34 to 15.03	2.52	0.37 to 17.35
Multiple Myeloma (C90)	1	15	0.42	0.05 to 3.38	0.45	0.06 to 3.61	3	1.11	0.12 to 10.75	1.08	0.11 to 10.52
Leukaemia (C91-C95, D45-D47)	6	33	0.86	0.35 to 2.11	0.94	0.38 to 2.30	13	1.59	0.58 to 4.35	1.94	0.69 to 5.42
Non-CLL (C91-C95, D45-D47, except C91.1)	6	23	1.24	0.49 to 3.15	1.36	0.53 to 3.48	7	2.76	0.91 to 8.38	2.95	0.95 to 9.11
Other and unspecified leukemia (C93 to C95)	1	1	3.22	0.20 to 52.54	6.15	0.35 to 108.18	0				
Myelodysplastic syndromes(MDS) (D46)	4	7	2.37	0.66 to 8.49	2.74	0.75 to 9.97	1	**22.44**	**1.71 to 293.99**	**24.27**	**2.08 to 283.07**
MDS, unspecified (D46.9)	4	3	**5.11**	**1.12 to 23.22**	**7.10**	**1.47 to 34.17**	0				
Other LH, uncertain (D47)	1	0					0				
Other LH thrombocythemia (D47.3)	1	0					0				
Not included in all cancers											
	p-yr 32 766	p-yr 185 283					p-yr 102 340				
Basal cell carcinoma of the skin (BCC) (C44)	33	149	1.12	0.76 to 1.66	1.20	0.81 to 1.77	58	**1.70**	**1.11 to 2.61**	**1.75**	**1.13 to 2.69**

Abbreviation: p-yr, person years.

Table F. Number of all cancers and select cancer sites any case among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 33 134	p-yr 181 196					p-yr 101 183				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	183	861	1.15	0.98 to 1.36	**1.20**	**1.02 to 1.42**	481	1.16	0.98 to 1.38	1.18	0.99 to 1.40
Lip, oral cavity, and pharynx (C00-C14)	2	16	0.61	0.14 to 2.72	0.64	0.14 to 2.87	2	2.93	0.40 to 21.50	2.64	0.36 to 19.45
Oesophagus (C15)	1	6	1.18	0.13 to 10.42	1.34	0.15 to 12.18	3	0.98	0.10 to 9.58	0.98	0.10 to 9.68
Stomach (C16)	5	18	1.47	0.53 to 4.04	1.72	0.61 to 4.84	7	2.29	0.72 to 7.26	2.30	0.72 to 7.35
Colon, rectum, and anus (C18-C21)	14	67	1.12	0.62 to 2.02	1.17	0.65 to 2.13	32	1.34	0.72 to 2.52	1.34	0.71 to 2.53
Bile and liver (C22-C24)	1	6	0.70	0.08 to 5.84	0.81	0.09 to 6.92	2	1.93	0.16 to 22.74	1.84	0.16 to 21.74
Pancreas (C25)	5	19	1.74	0.62 to 4.85	1.94	0.68 to 5.49	12	1.39	0.49 to 3.95	1.42	0.50 to 4.06
Lung and bronchus (C33-C34)	17	98	0.86	0.51 to 1.45	0.85	0.50 to 1.44	73	0.73	0.43 to 1.24	0.75	0.44 to 1.28
Bone (C40-C41)	1	1	5.51	0.29 to 105.91	4.89	0.26 to 91.92	2	1.74	0.15 to 19.58	1.64	0.15 to 18.67
Melanoma (C43)	7	37	0.92	0.40 to 2.09	0.99	0.43 to 2.27	20	1.16	0.49 to 2.76	1.12	0.47 to 2.68
Other cancer of skin (C44)	4	30	0.66	0.23 to 1.91	0.68	0.23 to 1.98	23	0.51	0.18 to 1.47	0.51	0.18 to 1.49
Soft tissue sarcoma (C49)	1	3	1.51	0.15 to 15.02	1.83	0.17 to 19.25	4	0.79	0.09 to 7.17	0.79	0.09 to 7.25
Breast (C50)	55	275	1.09	0.81 to 1.47	1.13	0.83 to 1.52	133	1.26	0.92 to 1.72	1.26	0.92 to 1.74
Vulva (C51)	2	4	2.56	0.45 to 14.57	2.72	0.46 to 16.06	1	7.15	0.63 to 80.94	8.26	0.73 to 94.00
Cervix uteri (C53)	8	21	1.91	0.82 to 4.45	1.92	0.82 to 4.49	14	1.72	0.72 to 4.12	1.68	0.70 to 4.01
Uterus (C54-C55)	10	28	1.99	0.93 to 4.23	2.10	0.98 to 4.50	24	1.28	0.61 to 2.68	1.35	0.64 to 2.85
Ovary (C56-C57)	7	44	1.06	0.46 to 2.41	1.10	0.48 to 2.51	19	1.12	0.47 to 2.66	1.17	0.49 to 2.80
Kidney (C64-C66)	7	34	1.23	0.53 to 2.84	1.29	0.55 to 3.02	17	1.26	0.52 to 3.06	1.32	0.54 to 3.21
Bladder (C67)	4	20	1.05	0.35 to 3.15	1.13	0.37 to 3.41	11	1.13	0.36 to 3.58	1.18	0.37 to 3.73
Brain and central nervous system (C70-C72, C75.1 and C75.3)	4	10	2.47	0.73 to 8.41	2.45	0.71 to 8.44	4	2.73	0.68 to 10.99	2.54	0.63 to 10.20
Thyroid gland (C73)	8	38	1.22	0.55 to 2.68	1.29	0.58 to 2.87	26	0.92	0.42 to 2.03	0.94	0.42 to 2.08
Cancer without specification of site (C80)	2	16	0.69	0.15 to 3.07	0.71	0.16 to 3.19	5	1.35	0.26 to 6.99	1.39	0.26 to 7.29
Lymphoid and haematopoietic	18	57	**1.78**	**1.03 to 3.09**	**1.98**	**1.14 to 3.46**	33	1.67	0.94 to 2.97	1.69	0.95 to 3.03

tissue (LH) (C81-C96, D45-D47)											
Hodgkin´s lymphoma (C81)	1	4	1.20	0.13 to 11.10	1.17	0.13 to 10.94	2	2.15	0.19 to 24.64	2.13	0.19 to 24.60
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	7	20	1.99	0.81 to 4.88	2.17	0.88 to 5.37	4	**6.21**	**1.78 to 21.66**	**5.83**	**1.66 to 20.40**
NHL, follicular (C82)	1	8	0.60	0.07 to 4.89	0.64	0.08 to 5.28	2	3.13	0.23 to 41.95	2.39	0.18 to 31.52
NHL, diffuse (C83)	3	12	1.56	0.42 to 5.79	1.86	0.49 to 7.00	2	4.71	0.77 to 28.84	5.21	0.83 to 32.54
NHL, peripheral T-cells (C84)	1	0					0				
NHL, unspecified (C85)	2	0					0				
Immunoproliferative diseases (C88)	2	6	2.05	0.39 to 10.77	2.09	0.39 to 11.33	4	1.86	0.33 to 10.34	2.20	0.38 to 12.60
Multiple Myeloma (C90)	4	10	1.90	0.58 to 6.25	2.00	0.60 to 6.62	8	1.48	0.44 to 4.92	1.44	0.43 to 4.83
Leukaemia (C91-C95, D45-D47)	4	17	1.52	0.49 to 4.72	1.93	0.61 to 6.09	15	0.81	0.27 to 2.44	0.89	0.29 to 2.71
Non-CLL (C91-C95, D45-D47, except C91.1)	3	12	1.66	0.44 to 6.20	1.99	0.53 to 7.58	13	0.72	0.20 to 2.53	0.77	0.22 to 2.73
Lymphoid leukemia (C91)	1	5	1.23	0.13 to 11.37	1.88	0.20 to 18.09	2	1.31	0.10 to 17.47	2.27	0.16 to 33.35
Chronic lymphocytic leukaemia (CLL)(C91.1)	1	5	1.23	0.13 to 11.37	1.88	0.20 to 18.09	2	1.31	0.10 to 17.47	2.27	0.16 to 33.35
Myelodysplastic syndromes (MDS) (D46)	3	3	**8.57**	**1.58 to 46.63**	**9.45**	**1.72 to 51.79**	1	8.31	0.85 to 81.40	8.13	0.83 to 79.51
MDS, unspecified (D46.9)	3	3	**8.57**	**1.58 to 46.63**	**9.45**	**1.72 to 51.79**	1	8.31	0.85 to 81.40	8.13	0.83 to 79.51
Not included in all cancers											
	p-yr 34 385	p-yr 186 406					p-yr 103 615				
Basal cell carcinoma of the skin (BCC) (C44)	41	208	1.00	0.71 to 1.40	1.05	0.74 to 1.48	96	1.26	0.87 to 1.82	1.30	0.90 to 1.88

Abbreviation: p-yr, person years.

Table G. Number of all cancers and cancer sites with any case among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 48 817	p-yr 281 694					p-yr 152 060				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	517	2839	1.05	0.95 to 1.15	1.07	0.97 to 1.18	1346	**1.18**	**1.06 to 1.31**	**1.21**	**1.09 to 1.34**
Lip, oral cavity, and pharynx (C00-C14)	11	64	0.83	0.43 to 1.60	0.82	0.43 to 1.59	29	1.31	0.63 to 2.72	1.38	0.66 to 2.88
Oesophagus (C15)	11	57	0.98	0.50 to 1.90	1.00	0.51 to 1.94	25	1.49	0.72 to 3.11	1.54	0.74 to 3.23
Stomach (C16)	17	125	0.78	0.47 to 1.32	0.77	0.45 to 1.30	86	0.61	0.36 to 1.03	0.60	0.35 to 1.01
Small intestine (C17)	1	16	0.27	0.04 to 2.05	0.26	0.03 to 2.02	6	0.93	0.09 to 9.48	1.05	0.10 to 11.08
Colon, rectum, and anus (C18-C21)	55	269	1.21	0.90 to 1.64	1.24	0.92 to 1.68	129	1.27	0.92 to 1.74	1.29	0.93 to 1.77
Bile and liver (C22-C24)	7	53	0.80	0.36 to 1.81	0.82	0.36 to 1.85	14	1.53	0.61 to 3.84	1.58	0.62 to 4.01
Pancreas (C25)	18	67	1.63	0.94 to 2.81	1.65	0.95 to 2.86	22	**2.60**	**1.38 to 4.90**	**2.69**	**1.42 to 5.09**
Nasal cavity and middle ear (C30)	1	4	1.92	0.18 to 20.26	1.70	0.16 to 18.00	1	14.24	0.27 to 755.38	13.29	0.29 to 614.04
Larynx (C32)	4	26	0.93	0.31 to 2.77	0.92	0.31 to 2.75	11	1.14	0.36 to 3.65	1.14	0.36 to 3.63
Lung and bronchus (C33-C34)	44	320	0.79	0.57 to 1.09	0.81	0.59 to 1.13	155	0.86	0.61 to 1.20	0.88	0.63 to 1.23
Bone (C40-C41)	1	13	0.42	0.05 to 3.30	0.40	0.05 to 3.16	1	6.32	0.22 to 179.65	5.63	0.19 to 164.71
Melanoma (C43)	9	57	0.91	0.44 to 1.89	0.93	0.45 to 1.94	17	1.57	0.70 to 3.53	1.62	0.72 to 3.66
Other cancer of skin (C44)	19	98	1.06	0.64 to 1.77	1.09	0.65 to 1.81	50	1.19	0.70 to 2.03	1.21	0.71 to 2.07
Kaposi´s sarcoma (C46)	1	8	0.66	0.08 to 5.69	0.70	0.08 to 6.31	5	0.51	0.06 to 4.59	0.57	0.06 to 5.12
Peritoneum (C48)	1	4	1.28	0.14 to 12.24	1.22	0.13 to 11.74	0				
Soft tissue sarcoma (C49)	2	22	0.45	0.10 to 1.98	0.45	0.10 to 1.97	6	1.19	0.23 to 6.29	1.28	0.24 to 6.75
Breast (C50)	3	9	1.58	0.40 to 6.16	1.57	0.40 to 6.17	5	2.03	0.47 to 8.74	2.16	0.50 to 9.43
Penis (C60)	2	11	1.00	0.21 to 4.79	1.11	0.23 to 5.36	3	2.14	0.32 to 14.22	1.90	0.28 to 12.95
Prostate (C61)	172	803	**1.27**	**1.07 to 1.51**	**1.32**	**1.11 to 1.57**	377	**1.43**	**1.19 to 1.72**	**1.47**	**1.22 to 1.77**
Testis (C62)	2	42	0.30	0.07 to 1.25	0.28	0.07 to 1.19	23	0.28	0.07 to 1.17	0.29	0.07 to 1.22
Kidney (C64-C66)	28	147	1.06	0.70 to 1.61	1.08	0.71 to 1.64	62	1.37	0.88 to 2.15	1.38	0.88 to 2.17
Bladder (C67)	35	191	0.97	0.67 to 1.41	0.99	0.68 to 1.44	110	0.96	0.66 to 1.41	1.01	0.69 to 1.49

Urinary organs, unspecified (C68)	1	2	2.68	0.21 to 33.75	2.22	0.17 to 29.77	1	3.36	0.20 to 55.46	3.54	0.22 to 57.47
Brain and central nervous system (C70-C72, C75.1 and C75.3)	4	60	0.42	0.15 to 1.17	0.41	0.15 to 1.16	29	0.48	0.16 to 1.38	0.47	0.16 to 1.38
Thyroid gland (C73)	7	43	0.96	0.42 to 2.20	0.94	0.41 to 2.17	18	1.33	0.54 to 3.29	1.36	0.55 to 3.37
Cancer without specification of site (C80)	6	51	0.79	0.33 to 1.90	0.78	0.32 to 1.87	29	0.65	0.27 to 1.58	0.71	0.29 to 1.74
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	55	253	1.24	0.92 to 1.68	1.27	0.94 to 1.73	118	**1.48**	**1.07 to 2.06**	**1.53**	**1.10 to 2.13**
Hodgkin´s lymphoma (C81)	2	19	0.59	0.13 to 2.60	0.56	0.13 to 2.49	9	0.82	0.17 to 4.05	0.78	0.16 to 3.86
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	24	82	**1.85**	**1.14 to 2.99**	**1.92**	**1.18 to 3.12**	46	1.60	0.97 to 2.66	1.65	0.99 to 2.74
NHL, follicular (C82)	3	16	0.95	0.27 to 3.41	1.03	0.28 to 3.73	9	1.14	0.31 to 4.25	1.19	0.32 to 4.44
NHL, diffuse (C83)	12	51	1.55	0.80 to 3.00	1.59	0.82 to 3.10	29	1.31	0.65 to 2.63	1.36	0.67 to 2.75
NHL, peripheral T-cells (C84)	5	10	**3.48**	**1.07 to 11.31**	**3.57**	**1.10 to 11.65**	5	3.31	0.86 to 12.68	3.41	0.87 to 13.28
NHL, unspecified (C85)	4	5	**5.00**	**1.20 to 20.87**	**5.00**	**1.19 to 20.97**	3	4.11	0.86 to 19.66	3.86	0.81 to 18.34
Immunoproliferative diseases (C88)	3	13	1.41	0.37 to 5.39	1.53	0.40 to 5.95	6	1.47	0.36 to 5.93	1.66	0.41 to 6.74
Multiple Myeloma (C90)	7	44	0.95	0.42 to 2.19	0.98	0.42 to 2.25	13	1.79	0.70 to 4.59	1.83	0.71 to 4.72
Leukaemia (C91-C95, D45-D47)	19	94	1.04	0.63 to 1.74	1.06	0.64 to 1.76	43	1.51	0.86 to 2.65	1.61	0.91 to 2.83
Non-CLL (C91-C95, D45-D47, except C91.1)	13	65	1.05	0.57 to 1.95	1.07	0.58 to 1.97	28	1.52	0.77 to 3.00	1.57	0.80 to 3.10
Lymphoid leukemia (C91)	7	41	0.85	0.38 to 1.94	0.86	0.38 to 1.96	19	1.45	0.56 to 3.70	1.61	0.62 to 4.20
Chronic lymphocytic leukaemia (CLL)(C91.1)	6	29	1.03	0.42 to 2.57	1.07	0.43 to 2.67	15	1.53	0.56 to 4.22	1.82	0.65 to 5.13
Other lymphoid leukemia (C91.2 to C91.9)	1	4	1.15	0.12 to 10.71	1.10	0.12 to 10.33	2	1.42	0.11 to 17.71	1.12	0.09 to 14.61
Myeloid leukemia (C92)	3	22	0.81	0.24 to 2.78	0.79	0.23 to 2.71	15	0.76	0.21 to 2.72	0.81	0.23 to 2.91
Acute myeloid leukemia (C92.0)	1	16	0.44	0.06 to 3.45	0.45	0.06 to 3.48	11	0.38	0.05 to 3.14	0.39	0.05 to 3.26
Other myeloid leukemia (C92.1 to C92.9)	2	6	1.51	0.30 to 7.58	1.42	0.28 to 7.15	4	1.96	0.35 to 10.84	2.19	0.40 to 12.07
Other and unspecified leukemia (C93 to C95)	1	5	0.86	0.10 to 7.73	0.92	0.10 to 8.36	0				
Myelodysplastic syndromes (MDS) (D46)	5	14	1.55	0.54 to 4.46	1.71	0.59 to 4.94	4	**4.13**	**1.10 to 15.55**	**4.19**	**1.11 to 15.90**
MDS, unspecified (D46.9)	5	9	2.27	0.74 to 6.92	2.59	0.84 to 7.97	1	**19.88**	**1.77 to 222.62**	**18.99**	**1.79 to 201.53**
Other LH, uncertain (D47)	3	8	2.78	0.65 to 11.87	2.81	0.66 to 11.94	4	2.04	0.45 to 9.18	1.88	0.42 to 8.44
Other LH thrombocythemia (D47.3)	3	0					0				

Not included in all cancers											
	p-yr 50 117	p-yr 289 385					p-yr 155 853				
Basal cell carcinoma of the skin (BCC) (C44)	81	344	1.27	0.99 to 1.64	**1.32**	**1.02 to 1.70**	146	**1.64**	**1.25 to 2.16**	**1.70**	**1.30 to 2.24**

Abbreviation: p-yr, person years.

Table H. Number of all cancers and cancer sites with any case among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits without and with stratification into categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	p-yr 49 094	p-yr 276 121					p-yr 147 818				
			Not stratified		Stratified			Not stratified		Stratified	
Cancers (ICD-10)	No of cancers	No of cancers	HR	95%CI	HR	95%CI	No of cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)	471	2492	1.08	0.98 to 1.20	**1.14**	**1.03 to 1.26**	1178	**1.16**	**1.04 to 1.29**	**1.21**	**1.09 to 1.35**
Lip, oral cavity, and pharynx (C00-C14)	5	39	0.68	0.26 to 1.76	0.73	0.28 to 1.90	12	1.20	0.42 to 3.43	1.18	0.41 to 3.39
Oesophagus (C15)	2	15	0.77	0.17 to 3.51	0.86	0.19 to 3.96	11	0.52	0.11 to 2.33	0.51	0.11 to 2.32
Stomach (C16)	13	71	1.01	0.55 to 1.85	1.08	0.58 to 1.98	28	1.33	0.69 to 2.56	1.45	0.74 to 2.81
Small intestine (C17)	3	9	2.77	0.70 to 11.02	3.15	0.79 to 12.56	7	1.48	0.37 to 5.84	1.56	0.38 to 6.35
Colon, rectum, and anus (C18-C21)	35	204	1.00	0.69 to 1.44	1.06	0.73 to 1.53	90	1.13	0.76 to 1.66	1.17	0.79 to 1.73
Bile and liver (C22-C24)	3	26	0.58	0.17 to 1.94	0.59	0.17 to 2.00	20	0.45	0.14 to 1.54	0.47	0.14 to 1.59
Pancreas (C25)	12	59	1.34	0.70 to 2.55	1.40	0.73 to 2.69	27	1.32	0.67 to 2.61	1.35	0.68 to 2.68
Lung and bronchus (C33-C34)	48	258	1.05	0.76 to 1.44	1.10	0.80 to 1.51	145	0.98	0.71 to 1.36	1.04	0.75 to 1.45
Bone (C40-C41)	3	8	2.11	0.52 to 8.56	1.88	0.47 to 7.58	5	1.74	0.41 to 7.34	1.84	0.43 to 7.82
Melanoma (C43)	15	81	0.97	0.55 to 1.70	1.05	0.59 to 1.85	40	1.14	0.63 to 2.06	1.16	0.64 to 2.11
Other cancer of skin (C44)	7	86	0.47	0.21 to 1.02	0.50	0.23 to 1.10	38	0.52	0.23 to 1.16	0.52	0.23 to 1.17
Peritoneum (C48)	1	11	0.40	0.05 to 3.16	0.41	0.05 to 3.23	7	0.45	0.06 to 3.63	0.45	0.06 to 3.67
Soft tissue sarcoma (C49)	4	15	1.73	0.55 to 5.51	1.89	0.60 to 6.03	9	1.32	0.40 to 4.33	1.39	0.42 to 4.57
Breast (C50)	158	731	**1.22**	**1.02 to 1.46**	**1.27**	**1.06 to 1.51**	321	**1.42**	**1.17 to 1.72**	**1.48**	**1.22 to 1.79**
Vulva (C51)	3	9	1.75	0.45 to 6.78	1.69	0.43 to 6.65	5	1.88	0.44 to 7.95	2.17	0.51 to 9.31
Vagina (C52)	1	2	3.08	0.23 to 41.26	3.33	0.24 to 46.49	3	0.91	0.09 to 8.84	1.36	0.13 to 13.87
Cervix uteri (C53)	14	81	0.93	0.52 to 1.67	0.90	0.51 to 1.62	31	1.33	0.71 to 2.51	1.36	0.72 to 2.56
Uterus (C54-C55)	22	115	1.14	0.71 to 1.84	1.22	0.76 to 1.97	59	1.07	0.65 to 1.74	1.12	0.68 to 1.83
Ovary (C56-C57)	20	145	0.83	0.52 to 1.35	0.88	0.54 to 1.43	64	0.91	0.55 to 1.50	0.97	0.58 to 1.60
Kidney (C64-C66)	21	94	1.46	0.89 to 2.39	1.62	0.99 to 2.67	41	1.46	0.86 to 2.48	1.60	0.94 to 2.73
Bladder (C67)	9	51	0.95	0.46 to 1.97	1.01	0.49 to 2.11	27	0.97	0.46 to 2.06	0.99	0.47 to 2.13
Brain and central nervous system (C70-C72, C75.1 and C75.3)	7	39	1.08	0.47 to 2.50	1.13	0.49 to 2.61	12	1.67	0.66 to 4.27	1.73	0.68 to 4.42
Thyroid gland (C73)	18	88	1.28	0.75 to 2.17	1.36	0.80 to 2.32	50	1.07	0.63 to 1.84	1.15	0.67 to 1.97

Cancer without specification of site (C80)	5	63	0.47	0.19 to 1.19	0.51	0.20 to 1.29	28	0.53	0.21 to 1.38	0.57	0.22 to 1.48
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)	42	166	1.40	0.98 to 1.99	**1.52**	**1.07 to 2.17**	81	**1.52**	**1.04 to 2.21**	**1.55**	**1.06 to 2.25**
Hodgkin´s lymphoma (C81)	4	15	1.22	0.39 to 3.79	1.29	0.41 to 4.01	5	2.43	0.64 to 9.24	2.44	0.64 to 9.29
Non-Hodgkin´s lymphoma (NHL) (C82-C85)	15	55	1.70	0.93 to 3.09	**1.92**	**1.05 to 3.50**	16	**2.98**	**1.46 to 6.07**	**3.08**	**1.51 to 6.32**
NHL, follicular (C82)	4	14	1.50	0.48 to 4.74	1.70	0.53 to 5.42	4	3.55	0.87 to 14.47	3.33	0.82 to 13.59
NHL, diffuse (C83)	5	31	1.11	0.42 to 2.95	1.28	0.48 to 3.44	11	1.46	0.50 to 4.24	1.58	0.54 to 4.63
NHL, peripheral T-cells (C84)	1	4	1.62	0.16 to 16.20	1.69	0.17 to 16.87	0				
NHL, unspecified (C85)	5	6	**5.24**	**1.47 to 18.61**	**5.50**	**1.55 to 19.58**	1	**13.72**	**1.59 to 118.27**	**14.46**	**1.66 to 125.87**
Immunoproliferative diseases (C88)	3	12	1.35	0.37 to 4.97	1.49	0.40 to 5.55	6	1.65	0.41 to 6.67	1.89	0.46 to 7.76
Multiple Myeloma (C90)	9	32	1.44	0.67 to 3.08	1.53	0.71 to 3.29	26	0.99	0.46 to 2.11	0.97	0.45 to 2.08
Leukaemia (C91-C95, D45-D47)	11	51	1.18	0.60 to 2.31	1.25	0.63 to 2.46	28	1.16	0.58 to 2.33	1.17	0.58 to 2.37
Non-CLL (C91-C95, D45-D47, except C91.1)	7	35	1.09	0.47 to 2.53	1.15	0.49 to 2.67	19	1.11	0.47 to 2.65	1.13	0.47 to 2.72
Lymphoid leukemia (C91)	5	21	1.22	0.44 to 3.34	1.30	0.47 to 3.59	9	1.60	0.53 to 4.78	1.60	0.53 to 4.85
Acute lymphoid leukemia (C91.0)	1	4	1.16	0.12 to 11.07	1.21	0.13 to 11.59	0				
Chronic lymphocytic leukaemia (CLL)(C91.1)	4	16	1.37	0.44 to 4.28	1.50	0.48 to 4.73	9	1.26	0.39 to 4.10	1.27	0.38 to 4.22
Myeloid leukemia (C92)	3	16	1.02	0.29 to 3.68	1.02	0.28 to 3.67	12	0.78	0.22 to 2.77	0.80	0.23 to 2.87
Acute myeloid leukemia (C92.0)	3	10	1.49	0.39 to 5.70	1.51	0.39 to 5.78	9	1.05	0.28 to 3.91	1.09	0.29 to 4.08
Myelodysplastic syndromes (MDS) (D46)	3	4	**5.87**	**1.20 to 28.80**	**6.28**	**1.26 to 31.22**	2	4.19	0.69 to 25.43	4.15	0.68 to 25.23
MDS, unspecified (D46.9)	3	3	**8.57**	**1.57 to 46.62**	**9.45**	**1.72 to 51.79**	2	4.19	0.69 to 25.43	4.15	0.68 to 25.23
Not included in all cancers											
	p-yr 50 898	p-yr 284 679					p-yr 151 910				
Basal cell carcinoma of the skin (BCC) (C44)	96	437	1.18	0.94 to 1.48	1.25	0.99 to 1.57	189	**1.46**	**1.14 to 1.86**	**1. 55**	**1.21 to 1.99**

Abbreviation: p-yr, person years.

Table I. Number of all cancers, and selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, split in four categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area			Cold reference area		
	p-yr 97 911	p-yr 557 815			p-yr 299 878		
Cancers (ICD-10)	No of cancers	No of cancers	HR	95%CI	No of cancers	HR	95%CI
All (C00-C97 and D45-D47)							
< 5 year	181	800	0.99	0.84 to 1.17	409	**1.20**	**1.01 to 1.43**
≥ 5 years, < 15 years	267	1557	**1.15**	**1.01 to 1.32**	806	**1.24**	**1.07 to 1.42**
≥ 15 years, < 24 years	271	1503	1.14	0.99 to 1.30	675	**1.22**	**1.06 to 1.41**
≥ 24 years	269	1471	1.09	0.95 to 1.25	634	**1.20**	**1.04 to 1.38**
Colon, rectum, and anus (C18-C21)							
< 5 year	14	62	1.03	0.57 to 1.87	33	1.16	0.62 to 2.16
≥ 5 years, < 15 years	21	136	1.09	0.68 to 1.77	62	1.31	0.79 to 2.17
≥ 15 years, < 24 years	32	141	1.40	0.94 to 2.10	61	**1.56**	**1.01 to 2.41**
≥ 24 years	23	134	1.03	0.65 to 1.62	63	1.05	0.65 to 1.69
Pancreas (C25)							
< 5 year	3	20	0.66	0.19 to 2.28	11	0.74	0.21 to 3.66
≥ 5 years, < 15 years	11	33	**2.65**	**1.28 to 5.50**	14	**3.58**	**1.56 to 8.21**
≥ 15 years, < 24 years	11	35	1.85	0.90 to 3.77	13	**2.58**	**1.14 to 5.85**
≥ 24 years	5	38	0.96	0.36 to 2.53	11	1.34	0.46 to 3.92
Lung and bronchus (C33-C34)							
< 5 year	24	103	1.00	0.63 to 1.57	55	1.20	0.74 to 1.94
≥ 5 years, < 15 years	23	167	1.02	0.65 to 1.61	112	0.76	0.49 to 1.20
≥ 15 years, < 24 years	19	158	0.76	0.47 to 1.25	76	0.79	0.47 to 1.31
≥ 24 years	26	150	0.94	0.61 to 1.45	57	1.32	0.83 to 2.10
Breast (C50)							
< 5 year	37	123	1.25	0.86 to 1.82	59	**1.61**	**1.07 to 2.44**
≥ 5 years, < 15 years	56	237	**1.63**	**1.21 to 2.21**	96	**2.23**	**1.60 to 3.12**
≥ 15 years, < 24 years	29	199	0.92	0.61 to 1.37	95	1.01	0.67 to 1.54
≥ 24 years	39	181	1.35	0.93 to 1.94	76	1.32	0.90 to 1.95
Prostate (C61)							
< 5 year	15	79	0.84	0.47 to 1.49	33	1.44	0.76 to 2.75
≥ 5 years, < 15 years	42	158	**1.77**	**1.22 to 2.57**	98	**1.60**	**1.09 to 2.34**
≥ 15 years, < 24 years	61	267	**1.42**	**1.06 to 1.91**	123	**1.50**	**1.09 to 2.05**
≥ 24 years	54	299	1.13	0.84 to 1.53	123	1.35	0.98 to 1.87
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)							
< 5 year	24	49	**2.37**	**1.42 to 3.96**	35	**1.86**	**1.10 to 3.13**
≥ 5 years, < 15 years	17	124	0.76	0.45 to 1.27	67	1.00	0.58 to 1.72
≥ 15 years, < 24 years	25	123	1.30	0.83 to 2.05	49	**1.65**	**1.01 to 2.70**
≥ 24 years	31	123	**1.57**	**1.04 to 2.37**	48	**1.79**	**1.13 to 2.84**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)							
< 5 year	10	11	**3.92**	**1.63 to 9.41**	11	**2.45**	**1.04 to 5.78**
≥ 5 years, < 15 years	8	39	1.27	0.57 to 2.81	20	1.64	0.68 to 3.97
≥ 15 years, < 24 years	9	47	1.40	0.66 to 2.96	15	2.18	0.90 to 5.28

≥ 24 years	12	40	**2.20**	**1.11 to 4.37**	16	**2.22**	**1.03 to 4.78**
Not included in all cancers							
Basal cell carcinoma of the skin (C44)	p-yr 101 014		p-yr 574 065		p-yr 307 763		
< 5 year	25	98	1.07	0.68 to 1.67	61	1.13	0.71 to 1.80
≥ 5 years, < 15 years	50	193	**1.72**	**1.24 to 2.38**	75	**2.40**	**1.67 to 3.44**
≥ 15 years, < 24 years	46	197	1.32	0.95 to 1.85	114	1.27	0.90 to 1.79
≥ 24 years	56	293	1.07	0.79 to 1.44	85	**1.71**	**1.22 to 2.40**

Abbreviation: p-yr, person years.

Table J. Number of all cancers, and selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, split in four categories of cumulative years of residence in the respective areas.

	Geothermal heating area	Warm reference area			Cold reference area		
	p-yr 65 169	p-yr 362 298			p-yr 201 705		
Cancers (ICD-10)	No of cancers	No of cancers	HR	95%CI	No of cancers	HR	95%CI
All (C00-C97 and D45-D47)							
< 5 year	117	456	1.16	0.94 to 1.43	255	**1.29**	**1.03 to 1.60**
≥ 5 years, < 15 years	91	539	1.15	0.91 to 1.45	321	1.09	0.86 to 1.38
≥ 15 years, < 24 years	38	193	1.32	0.91 to 1.90	113	1.12	0.77 to 1.62
≥ 24 years	126	657	1.11	0.91 to 1.36	270	**1.32**	**1.06 to 1.63**
Colon, rectum, and anus (C18-C21)							
< 5 year	11	38	1.33	0.67 to 2.65	24	1.29	0.63 to 2.64
≥ 5 years, < 15 years	7	49	1.17	0.51 to 2.68	23	1.27	0.53 to 3.01
≥ 15 years, < 24 years	1	15	0.38	0.05 to 2.97	7	0.60	0.07 to 4.92
≥ 24 years	13	61	1.20	0.64 to 2.23	24	1.53	0.78 to 3.02
Pancreas (C25)							
< 5 year	1	8	0.55	0.07 to 4.47	6	0.47	0.06 to 3.91
≥ 5 years, < 15 years	7	11	**5.18**	**1.85 to 14.53**	7	**4.90**	**1.65 to 14.53**
≥ 15 years, < 24 years	1	3	2.47	0.22 to 27.76	2	2.68	0.23 to 31.74
≥ 24 years	2	14	1.25	0.27 to 5.89	4	1.71	0.31 to 9.52
Lung and bronchus (C33-C34)							
< 5 year	19	73	1.10	0.66 to 1.85	38	1.41	0.81 to 2.45
≥ 5 years, < 15 years	4	60	0.49	0.18 to 1.38	48	**0.35**	**0.12 to 0.96**
≥ 15 years, < 24 years	7	20	2.45	0.96 to 6.23	14	1.56	0.62 to 3.97
≥ 24 years	10	56	0.91	0.46 to 1.82	26	1.06	0.51 to 2.20
Breast (C50)							
< 5 year	19	63	1.29	0.76 to 2.17	34	1.47	0.84 to 2.59
≥ 5 years, < 15 years	17	81	1.38	0.80 to 2.37	44	1.57	0.90 to 2.77
≥ 15 years, < 24 years	3	33	0.62	0.19 to 2.09	19	0.62	0.18 to 2.12
≥ 24 years	17	100	1.07	0.63 to 1.84	36	1.26	0.70 to 2.25
Prostate (C61)							
< 5 year	13	68	0.88	0.47 to 1.64	30	1.41	0.71 to 2.80
≥ 5 years, < 15 years	11	60	1.27	0.64 to 2.52	42	1.00	0.50 to 2.00
≥ 15 years, < 24 years	9	34	2.10	0.93 to 4.73	20	1.49	0.66 to 3.33
≥ 24 years	24	126	1.18	0.75 to 1.86	46	1.60	0.97 to 2.64
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)							
< 5 year	14	27	**2.62**	**1.33 to 5.14**	18	**2.21**	**1.09 to 4.46**
≥ 5 years, < 15 years	5	44	0.74	0.29 to 1.92	31	0.62	0.24 to 1.60
≥ 15 years, < 24 years	2	22	0.65	0.15 to 2.87	7	0.96	0.19 to 4.72
≥ 24 years	16	50	**1.91**	**1.05 to 3.47**	16	**2.93**	**1.44 to 5.97**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)							
< 5 year	7	8	**4.02**	**1.40 to 11.51**	7	2.86	0.99 to 8.26
≥ 5 years, < 15 years	2	15	1.05	0.23 to 4.85	8	1.05	0.20 to 5.43
≥ 15 years, < 24 years	2	8	2.23	0.43 to 11.71	2	8.72	0.78 to 98.12

≥ 24 years	6	18	2.03	0.76 to 5.43	3	**6.15**	**1.42 to 26.61**
Not included in all cancers							
Basal cell carcinoma of the skin (C44)	p-yr 67 151		p-yr 371 689		p-yr 206 015		
< 5 year	18	70	1.09	0.64 to 1.86	47	1.09	0.63 to 1.87
≥ 5 years, < 15 years	20	95	1.30	0.79 to 2.14	43	1.68	0.98 to 2.88
≥ 15 years, < 24 years	8	50	0.80	0.37 to 1.72	29	0.86	0.39 to 1.90
≥ 24 years	28	142	1.06	0.70 to 1.61	35	**2.11**	**1.28 to 2.48**

Abbreviation: p-yr, person years.

Table K. Number of all cancers, and selected cancer sites among men and women combined, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)											
< 20	63	348	1.00	0.76 to 1.32	1.06	0.80 to 1.40	165	1.13	0.85 to 1.52	1.18	0.88 to 1.57
< 25	109	582	1.13	0.92 to 1.40	1.21	0.97 to 1.49	275	**1.29**	**1.03 to 1.62**	**1.33**	**1.07 to 1.67**
< 30	164	951	1.06	0.89 to 1.26	1.13	0.95 to 1.35	452	1.19	0.99 to 1.42	**1.24**	**1.04 to 1.49**
< 35	259	1433	1.06	0.93 to 1.22	1.12	0.97 to 1.28	658	**1.26**	**1.09 to 1.45**	**1.31**	**1.13 to 1.52**
< 40	357	2022	1.00	0.89 to 1.12	1.06	0.94 to 1.19	937	**1.16**	**1.02 to 1.31**	**1.21**	**1.07 to 1.37**
≥ 40	631	3309	**1.11**	**1.01 to 1.21**	**1.13**	**1.04 to 1.24**	1587	**1.16**	**1.06 to 1.27**	**1.19**	**1.09 to 1.31**
Colon, rectum, and anus (C18-C21)											
< 20	4	17	1.49	0.47 to 4.74	1.55	0.48 to 4.94	6	1.90	0.54 to 6.76	2.00	0.56 to 7.14
< 25	8	33	1.64	0.73 to 3.72	1.74	0.77 to 3.94	9	**3.15**	**1.20 to 8.24**	**3.31**	**1.26 to 8.68**
< 30	12	53	1.60	0.83 to 3.10	1.74	0.89 to 3.38	20	**2.05**	**1.00 to 4.21**	**2.22**	**1.08 to 4.59**
< 35	19	86	1.39	0.83 to 2.34	1.50	0.89 to 2.54	37	1.69	0.97 to 2.94	**1.79**	**1.02 to 3.12**
< 40	26	125	1.30	0.83 to 2.02	1.44	0.92 to 2.25	66	1.23	0.78 to 1.94	1.32	0.83 to 2.09
≥ 40	64	348	1.07	0.81 to 1.41	1.09	0.83 to 1.44	153	1.19	0.89 to 1.59	1.19	0.89 to 1.60
Pancreas (C25)											
< 20	0	1					2				
< 25	0	2					5				
< 30	1	16	0.42	0.05 to 3.26	0.45	0.06 to 3.52	5	0.64	0.07 to 5.55	0.62	0.07 to 5.40
< 35	3	25	0.78	0.23 to 2.66	0.83	0.24 to 2.86	9	1.13	0.31 to 4.20	1.19	0.32 to 4.43
< 40	5	36	0.93	0.35 to 2.45	1.00	0.38 to 2.66	16	1.02	0.37 to 2.80	1.06	0.39 to 2.92
≥ 40	25	90	**1.73**	**1.08 to 2.74**	**1.72**	**1.08 to 2.74**	33	**2.21**	**1.31 to 3.73**	**2.28**	**1.34 to 3.86**
Breast (C50)											
< 20	16	62	1.29	0.73 to 2.29	1.49	0.83 to 2.65	33	1.41	0.78 to 2.57	1.55	0.85 to 2.84
< 25	29	117	1.49	0.98 to 2.29	**1.70**	**1.11 to 2.62**	64	1.51	0.97 to 2.35	**1.58**	**1.02 to 2.46**
< 30	41	180	1.36	0.95 to 1.94	**1.50**	**1.05 to 2.14**	110	1.19	0.83 to 1.71	1.28	0.89 to 1.84
< 35	61	272	1.25	0.93 to 1.67	**1.35**	**1.01 to 1.80**	144	1.30	0.96 to 1.76	**1.37**	**1.01 to 1.85**
< 40	84	397	1.15	0.90 to 1.47	1.24	0.97 to 1.59	179	**1.37**	**1.06 to 1.78**	**1.46**	**1.13 to 1.90**

≥ 40	77	343	**1.32**	**1.02 to 1.70**	**1.32**	**1.02 to 1.71**	147	**1.44**	**1.09 to 1.90**	**1.48**	**1.12 to 1.95**
Prostate (C61)											
< 20	4	7	2.85	0.76 to 10.65	3.28	0.87 to 12.42	3	3.97	0.85 to 18.56	4.22	0.90 to 19.67
< 25	5	18	1.49	0.53 to 4.20	1.57	0.55 to 4.44	9	1.86	0.61 to 5.67	1.92	0.63 to 5.87
< 30	10	39	1.47	0.71 to 3.04	1.57	0.76 to 3.25	25	1.37	0.65 to 2.88	1.44	0.68 to 3.04
< 35	17	111	0.89	0.52 to 1.52	0.96	0.56 to 1.64	56	1.02	0.59 to 1.78	1.09	0.63 to 1.91
< 40	34	209	0.87	0.60 to 1.27	0.97	0.66 to 1.41	100	1.12	0.75 to 1.67	1.17	0.78 to 1.75
≥ 40	138	594	**1.45**	**1.19 to 1.76**	**1.47**	**1.21 to 1.79**	277	**1.53**	**1.24 to 1.88**	**1.56**	**1.27 to 1.92**
Kidney (C64-C66)											
< 20	2	15	0.81	0.17 to 3.73	0.90	0.19 to 4.16	5	1.68	0.29 to 9.84	1.87	0.31 to 11.18
< 25	2	22	0.59	0.13 to 2.62	0.65	0.15 to 2.87	11	0.62	0.14 to 2.79	0.62	0.14 to 2.83
< 30	4	42	0.59	0.20 to 1.68	0.60	0.21 to 1.73	23	0.59	0.20 to 1.69	0.60	0.21 to 1.73
< 35	13	61	1.21	0.65 to 2.25	1.23	0.66 to 2.31	29	1.45	0.75 to 2.79	1.53	0.79 to 2.95
< 40	18	87	1.12	0.66 to 1.90	1.18	0.69 to 2.00	41	1.32	0.76 to 2.30	1.39	0.80 to 2.43
≥ 40	31	154	1.28	0.86 to 1.91	1.35	0.90 to 2.03	62	1.45	0.94 to 2.24	1.54	0.99 to 2.39
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)											
< 20	6	32	1.03	0.42 to 2.55	1.06	0.43 to 2.62	21	0.98	0.38 to 2.49	0.99	0.39 to 2.53
< 25	13	49	1.49	0.78 to 2.81	1.57	0.83 to 2.97	37	1.20	0.63 to 2.28	1.21	0.63 to 2.31
< 30	19	98	1.21	0.73 to 2.02	1.29	0.77 to 2.16	48	1.43	0.83 to 2.47	1.45	0.84 to 2.51
< 35	28	141	1.21	0.79 to 1.85	1.27	0.83 to 1.94	62	**1.62**	**1.02 to 2.57**	**1.66**	**1.05 to 2.64**
< 40	33	183	1.05	0.71 to 1.54	1.12	0.76 to 1.64	86	1.21	0.81 to 1.81	1.25	0.83 to 1.87
≥ 40	64	236	**1.50**	**1.13 to 2.00**	**1.56**	**1.17 to 2.09**	113	**1.70**	**1.25 to 2.32**	**1.78**	**1.30 to 2.43**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)											
< 20	3	7	2.64	0.61 to 11.35	2.90	0.67 to 12.57	6	1.87	0.43 to 8.17	1.96	0.44 to 8.63
< 25	6	14	**2.97**	**1.06 to 8.30**	**3.32**	**1.18 to 9.30**	11	2.33	0.79 to 6.84	2.33	0.80 to 6.83
< 30	11	33	**2.31**	**1.12 to 4.78**	**2.58**	**1.24 to 5.37**	19	**2.46**	**1.11 to 5.42**	**2.57**	**1.16 to 5.69**
< 35	16	48	**2.26**	**1.23 to 4.14**	**2.48**	**1.34 to 4.56**	22	**2.67**	**1.36 to 5.22**	**2.80**	**1.42 to 5.51**
< 40	18	60	**1.92**	**1.09 to 3.36**	**2.14**	**1.22 to 3.75**	31	**1.93**	**1.06 to 3.50**	**2.00**	**1.10 to 3.64**
≥ 40	21	77	**1.66**	**1.00 to 2.75**	**1.74**	**1.05 to 2.89**	31	**2.08**	**1.17 to 3.68**	**2.22**	**1.24 to 3.94**
Not included in all cancers											
Basal cell carcinoma of the skin (C44)											
< 20	14	70	1.02	0.56 to 1.84	1.12	0.61 to 2.03	35	1.14	0.61 to 2.11	1.25	0.67 to 2.33

< 25	25	113	1.18	0.75 to 1.85	1.29	0.82 to 2.02	50	1.54	0.95 to 2.49	**1.69**	**1.04 to 2.75**
< 30	42	163	1.38	0.97 to 1.96	**1.50**	**1.05 to 2.14**	75	**1.72**	**1.18 to 2.52**	**1.84**	**1.26 to 2.70**
< 35	52	234	1.17	0.86 to 1.61	1.28	0.93 to 1.74	102	**1.56**	**1.11 to 2.18**	**1.66**	**1.19 to 2.33**
< 40	76	314	1.25	0.97 to 1.63	**1.36**	**1.04 to 1.76**	138	**1.60**	**1.21 to 2.12**	**1.71**	**1.29 to 2.27**
≥ 40	101	467	1.20	0.96 to 1.50	1.24	0.99 to 1.55	197	**1.47**	**1.16 to 1.87**	**1.54**	**1.21 to 1.96**

Table L. Number of all cancers, and selected cancer sites among men in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)											
< 20	19	133	0.86	0.52 to 1.42	0.87	0.53 to 1.44	57	1.00	0.59 to 1.68	1.01	0.60 to 1.71
< 25	32	228	0.86	0.59 to 1.26	0.88	0.60 to 1.29	93	1.10	0.74 to 1.65	1.15	0.76 to 1.72
< 30	48	386	0.77	0.57 to 1.05	0.80	0.59 to 1.09	166	0.98	0.71 to 1.35	1.02	0.74 to 1.41
< 35	91	628	0.85	0.68 to 1.07	0.88	0.70 to 1.11	276	1.09	0.86 to 1.39	1.15	0.91 to 1.46
< 40	147	929	0.91	0.76 to 1.09	0.95	0.79 to 1.14	422	1.12	0.93 to 1.35	1.17	0.97 to 1.42
≥ 40	370	1910	**1.12**	**1.00 to 1.26**	**1.13**	**1.01 to 1.27**	924	**1.20**	**1.06 to 1.35**	**1.22**	**1.08 to 1.38**
Colon, rectum, and anus (C18-C21)											
< 20	2	10	1.26	0.25 to 6.40	1.32	0.26 to 6.72	2	3.11	0.41 to 23.75	3.66	0.48 to 28.07
< 25	5	19	1.85	0.64 to 5.32	1.90	0.66 to 5.46	3	**7.44**	**1.52 to 36.38**	**7.95**	**1.64 to 38.61**
< 30	5	32	1.08	0.40 to 2.89	1.13	0.42 to 3.04	9	2.00	0.66 to 6.02	2.20	0.73 to 6.66
< 35	11	54	1.26	0.64 to 2.48	1.36	0.69 to 2.69	21	1.78	0.85 to 3.69	1.84	0.88 to 3.82
< 40	17	79	1.36	0.78 to 2.36	1.50	0.86 to 2.61	38	1.46	0.82 to 2.60	1.56	0.87 to 2.79
≥ 40	38	190	1.17	0.81 to 1.68	1.16	0.81 to 1.68	91	1.19	0.81 to 1.74	1.16	0.79 to 1.70
Pancreas (C25)											
< 20	0	0					1				
< 25	0	1					2				
< 30	1	8	0.74	0.09 to 6.22	0.76	0.09 to 6.35	2	1.65	0.13 to 20.47	1.90	0.15 to 24.00
< 35	2	11	0.95	0.20 to 4.47	0.96	0.20 to 4.54	5	1.66	0.29 to 9.35	1.83	0.31 to 10.67
< 40	4	19	1.28	0.41 to 3.98	1.36	0.44 to 4.23	8	1.86	0.55 to 6.31	1.98	0.58 to 6.81
≥ 40	14	48	1.78	0.95 to 3.34	1.76	0.94 to 3.32	14	**2.95**	**1.39 to 6.26**	**2.98**	**1.40 to 6.36**
Breast (C50)											
< 20	0	0					0				
< 25	0	0					1				
< 30	1	0					2	1.81	0.15 to 22.16	2.04	0.16 to 25.93
< 35	2	2	4.33	0.53 to 35.55	4.30	0.52 to 35.25	2	3.98	0.50 to 31.72	4.67	0.57 to 38.60
< 40	3	2	6.32	0.93 to 42.95	**7.05**	**1.03 to 48.12**	2	5.38	0.82 to 35.18	6.21	0.91 to 42.24

≥ 40	0	7					3				
Prostate (C61)										
< 20	4	7	2.85	0.76 to 10.65	3.28	0.87 to 12.42	3	3.97	0.85 to 18.56	4.22	0.90 to 19.67
< 25	5	18	1.49	0.53 to 4.20	1.57	0.55 to 4.44	9	1.86	0.61 to 5.67	1.92	0.63 to 5.87
< 30	10	39	1.47	0.71 to 3.04	1.57	0.76 to 3.25	25	1.37	0.65 to 2.88	1.44	0.68 to 3.04
< 35	17	111	0.89	0.52 to 1.52	0.96	0.56 to 1.64	56	1.02	0.59 to 1.78	1.09	0.63 to 1.91
< 40	34	209	0.87	0.60 to 1.27	0.97	0.66 to 1.41	100	1.12	0.75 to 1.67	1.17	0.78 to 1.75
≥ 40	138	594	**1.45**	**1.19 to 1.76**	**1.47**	**1.21 to 1.79**	277	**1.53**	**1.24 to 1.88**	**1.56**	**1.27 to 1.92**
Kidney (C64-C66)										
< 20	1	12	0.55	0.07 to 4.48	0.62	0.08 to 5.06	4	1.05	0.10 to 11.72	1.13	0.10 to 12.63
< 25	1	15	0.41	0.05 to 3.20	0.45	0.06 to 3.54	6	0.53	0.06 to 4.42	0.58	0.07 to 4.81
< 30	1	28	0.21	0.03 to 1.56	0.22	0.03 to 1.62	13	0.25	0.03 to 1.92	0.26	0.03 to 2.00
< 35	6	37	0.89	0.36 to 2.18	0.88	0.36 to 2.16	17	1.14	0.45 to 2.89	1.21	0.48 to 3.07
< 40	11	55	1.05	0.53 to 2.06	1.09	0.55 to 2.14	24	1.39	0.68 to 2.84	1.48	0.72 to 3.04
≥ 40	17	92	1.07	0.63 to 1.84	1.09	0.64 to 1.88	38	1.35	0.76 to 2.41	1.37	0.77 to 2.45
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)										
< 20	2	19	0.67	0.15 to 3.03	0.67	0.15 to 3.03	14	0.43	0.10 to 1.92	0.43	0.10 to 1.92
< 25	4	29	0.76	0.26 to 2.23	0.80	0.27 to 2.33	22	0.60	0.20 to 1.76	0.62	0.21 to 1.84
< 30	6	56	0.68	0.29 to 1.63	0.72	0.30 to 1.72	31	0.68	0.28 to 1.65	0.70	0.29 to 1.71
< 35	11	87	0.78	0.41 to 1.49	0.81	0.42 to 1.54	41	0.96	0.48 to 1.91	1.00	0.50 to 1.99
< 40	14	115	0.71	0.40 to 1.25	0.74	0.42 to 1.31	57	0.78	0.44 to 1.41	0.82	0.46 to 1.48
≥ 40	41	138	**1.68**	**1.17 to 2.43**	**1.71**	**1.18 to 2.48**	61	**2.19**	**1.44 to 3.31**	**2.27**	**1.49 to 3.46**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)										
< 20	2	6	2.23	0.40 to 12.59	2.47	0.44 to 13.94	4	2.07	0.29 to 14.68	2.21	0.30 to 16.39
< 25	3	9	2.11	0.53 to 8.43	2.46	0.61 to 9.89	9	1.20	0.30 to 4.77	1.26	0.32 to 5.02
< 30	4	20	1.48	0.48 to 4.60	1.68	0.54 to 5.24	15	0.99	0.31 to 3.08	1.03	0.33 to 3.25
< 35	7	32	1.53	0.64 to 3.65	1.71	0.71 to 4.11	18	1.32	0.54 to 3.20	1.40	0.57 to 3.42
< 40	9	40	1.46	0.68 to 3.14	1.62	0.75 to 3.51	25	1.14	0.53 to 2.46	1.17	0.54 to 2.53
≥ 40	15	42	**2.16**	**1.15 to 4.04**	**2.14**	**1.14 to 4.02**	21	**2.22**	**1.10 to 4.51**	**2.31**	**1.13 to 4.70**
Not included in all cancers										
Basal cell carcinoma of the skin (C44)										
< 20	6	23	1.38	0.53 to 3.57	1.45	0.56 to 3.78	11	1.62	0.60 to 4.41	1.61	0.59 to 4.41

< 25	10	45	1.36	0.66 to 2.81	1.45	0.70 to 2.99	15	2.20	0.97 to 4.98	**2.28**	**1.00 to 5.20**
< 30	17	66	1.63	0.93 to 2.88	**1.80**	**1.02 to 3.16**	26	**2.11**	**1.14 to 3.90**	**2.18**	**1.18 to 4.03**
< 35	23	102	1.27	0.79 to 2.03	1.39	0.87 to 2.24	36	**2.02**	**1.20 to 3.42**	**2.14**	**1.26 to 3.62**
< 40	34	133	1.38	0.93 to 2.05	**1.51**	**1.02 to 2.24**	47	**2.22**	**1.42 to 3.45**	**2.32**	**1.49 to 3.62**
≥ 40	47	211	1.21	0.87 to 1.68	1.24	0.89 to 1.72	99	1.38	0.97 to 1.95	1.41	0.99 to 2.01

Table M. Number of selected cancer sites among women in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)											
< 20	44	215	1.09	0.77 to 1.52	1.20	0.85 to 1.68	108	1.20	0.84 to 1.70	1.26	0.88 to 1.79
< 25	77	354	**1.32**	**1.02 to 1.70**	**1.45**	**1.12 to 1.88**	182	**1.39**	**1.06 to 1.82**	**1.43**	**1.09 to 1.87**
< 30	116	565	**1.27**	**1.03 to 1.56**	**1.38**	**1.12 to 1.70**	286	**1.31**	**1.05 to 1.62**	**1.37**	**1.10 to 1.70**
< 35	168	805	**1.22**	**1.03 to 1.46**	**1.31**	**1.10 to 1.56**	382	**1.37**	**1.15 to 1.65**	**1.43**	**1.19 to 1.72**
< 40	210	1093	1.08	0.93 to 1.26	**1.17**	**1.00 to 1.36**	515	**1.20**	**1.02 to 1.41**	**1.26**	**1.08 to 1.49**
≥ 40	261	1399	1.09	0.95 to 1.25	1.13	0.99 to 1.30	663	1.11	0.96 to 1.28	**1.16**	**1.01 to 1.35**
Colon, rectum, and anus (C18-C21)											
< 20	2	7	1.82	0.35 to 9.55	2.03	0.38 to 10.81	4	1.45	0.27 to 7.99	1.56	0.28 to 8.73
< 25	3	14	1.43	0.39 to 5.26	1.70	0.46 to 6.29	6	1.74	0.43 to 7.06	1.77	0.44 to 7.19
< 30	7	21	2.44	0.98 to 6.05	**2.78**	**1.11 to 6.92**	11	2.24	0.86 to 5.84	2.42	0.92 to 6.39
< 35	8	32	1.61	0.71 to 3.65	1.75	0.77 to 3.98	16	1.67	0.71 to 3.93	1.81	0.77 to 4.29
< 40	9	46	1.19	0.56 to 2.51	1.32	0.62 to 2.79	28	0.99	0.46 to 2.10	1.05	0.49 to 2.25
≥ 40	26	158	0.97	0.63 to 1.48	1.02	0.67 to 1.57	62	1.19	0.75 to 1.88	1.25	0.79 to 1.99
Pancreas (C25)											
< 20	0	1					1				
< 25	0	1					3				
< 30	0	8					3				
< 35	1	14	0.56	0.07 to 4.39	0.61	0.08 to 4.82	4	0.84	0.09 to 7.64	0.80	0.09 to 7.26
< 40	1	17	0.45	0.06 to 3.51	0.50	0.06 to 3.88	8	0.36	0.05 to 2.92	0.37	0.05 to 2.98
≥ 40	11	42	1.68	0.84 to 3.36	1.72	0.85 to 3.46	19	1.69	0.80 to 3.56	1.75	0.83 to 3.72
Breast (C50)											
< 20	16	62	1.29	0.73 to 2.29	1.49	0.83 to 2.65	33	1.41	0.78 to 2.57	1.55	0.85 to 2.84
< 25	29	117	1.49	0.98 to 2.29	**1.70**	**1.11 to 2.62**	63	1.53	0.98 to 2.39	**1.60**	**1.03 to 2.49**
< 30	40	180	1.32	0.92 to 1.89	**1.46**	**1.02 to 2.09**	108	1.18	0.82 to 1.70	1.27	0.88 to 1.84
< 35	59	270	1.22	0.91 to 1.63	1.31	0.98 to 1.76	142	1.27	0.94 to 1.73	1.34	0.99 to 1.82
< 40	81	395	1.11	0.87 to 1.43	1.21	0.94 to 1.55	177	**1.33**	**1.02 to 1.74**	**1.42**	**1.09 to 1.85**

≥ 40	77	336	**1.34**	**1.04 to 1.74**	**1.35**	**1.04 to 1.75**	144	**1.47**	**1.11 to 1.94**	**1.50**	**1.14 to 1.99**
Kidney (C64-C66)											
< 20	1	3	1.53	0.14 to 16.29	1.46	1.14 to 15.65	1	3.08	0.19 to 51.25	3.12	0.18 to 54.04
< 25	1	7	1.02	0.12 to 9.01	1.20	0.13 to 10.89	5	0.77	0.09 to 6.70	0.64	0.07 to 5.58
< 30	3	14	1.44	0.39 to 5.34	1.57	0.41 to 5.95	10	1.01	0.28 to 3.69	1.01	0.27 to 3.71
< 35	7	24	1.72	0.71 to 4.18	1.87	0.76 to 4.57	12	1.87	0.73 to 4.76	1.88	0.74 to 4.82
< 40	7	32	1.26	0.54 to 2.96	1.36	0.58 to 3.20	17	1.24	0.51 to 3.00	1.30	0.54 to 3.17
≥ 40	14	62	1.58	0.86 to 2.90	1.79	0.97 to 3.29	24	1.59	0.82 to 3.08	1.90	0.97 to 3.72
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)											
< 20	4	13	1.47	0.46 to 4.70	1.57	0.49 to 5.06	7	2.01	0.58 to 6.98	1.93	0.55 to 6.72
< 25	9	20	**2.51**	**1.09 to 5.79**	**2.70**	**1.17 to 6.25**	15	2.04	0.88 to 4.74	1.97	0.85 to 4.58
< 30	13	42	1.89	0.98 to 3.64	**2.10**	**1.09 to 4.05**	17	**2.68**	**1.29 to 5.57**	**2.66**	**1.27 to 5.56**
< 35	17	54	**1.91**	**1.07 to 3.39**	**2.06**	**1.16 to 3.68**	21	**2.77**	**1.45 to 5.29**	**2.73**	**1.42 to 5.22**
< 40	19	68	1.62	0.95 to 2.76	**1.79**	**1.05 to 3.05**	29	**2.00**	**1.12 to 3.59**	**2.01**	**1.12 to 3.61**
≥ 40	23	98	1.28	0.80 to 2.04	1.38	0.86 to 2.22	52	1.28	0.78 to 2.09	1.31	0.80 to 2.15
Non-Hodgkin´s lymphoma (NHL) (C82-C85)											
< 20	1	1	4.67	0.26 to 83.93	4.98	0.26 to 93.94	2	1.55	0.14 to 17.43	1.39	0.12 to 15.77
< 25	3	5	**4.93**	**1.06 to 22.85**	**5.22**	**1.12 to 24.28**	2	**6.44**	**1.04 to 39.99**	5.61	0.91 to 34.51
< 30	7	13	**3.61**	**1.35 to 9.66**	**3.96**	**1.48 to 10.56**	4	**6.96**	**2.01 to 24.16**	**7.42**	**2.09 to 26.34**
< 35	9	16	**3.83**	**1.59 to 9.28**	**4.15**	**1.71 to 10.09**	4	**8.53**	**2.59 to 28.10**	**8.52**	**2.57 to 28.27**
< 40	9	20	**2.92**	**1.26 to 6.77**	**3.25**	**1.40 to 7.55**	6	**5.56**	**1.95 to 15.88**	**5.64**	**1.96 to 16.21**
≥ 40	6	35	1.08	0.44 to 2.64	1.22	0.49 to 3.00	10	1.75	0.63 to 4.84	1.88	0.67 to 5.30
Not included in all cancers											
Basal cell carcinoma of the skin (C44)											
< 20	8	47	0.85	0.40 to 1.84	0.96	0.44 to 2.09	24	0.94	0.42 to 2.09	1.06	0.48 to 2.37
< 25	15	68	1.10	0.62 to 1.95	1.22	0.68 to 2.18	35	1.28	0.70 to 2.36	1.43	0.78 to 2.63
< 30	25	97	1.26	0.80 to 1.99	1.37	0.87 to 2.16	49	1.52	0.94 to 2.47	**1.67**	**1.03 to 2.72**
< 35	29	132	1.11	0.73 to 1.68	1.20	0.79 to 1.82	66	1.31	0.85 to 2.03	1.43	0.92 to 2.23
< 40	42	181	1.17	0.82 to 1.65	1.26	0.89 to 1.79	91	1.30	0.90 to 1.87	1.40	0.97 to 2.03
≥ 40	54	256	1.18	0.87 to 1.60	1.23	0.91 to 1.67	98	**1.54**	**1.10 to 2.15**	**1.62**	**1.16 to 2.27**

Table N. Number of selected cancer sites among men and women combined in the geothermal heating areas, hazard ratio (HR), 95% confidence intervals (CI) compared with the populations in warm reference area and cold reference area, applying five years latency time, adjusted for age, gender, education, type of housing, and smoking habits, without and with stratification into categories of cumulative years of residence, restricted on different age categories in the respective areas.

	Geothermal heating area	Warm reference area					Cold reference area				
	No of	No of	Not stratified		Stratified		No of	Not stratified		Stratified	
Cancers (ICD-10)	cancers	cancers	HR	95%CI	HR	95%CI	cancers	HR	95%CI	HR	95%CI
All (C00-C97, D45-D47)											
< 20	40	214	1.03	0.73 to 1.47	1.11	0.78 to 1.58	113	1.05	0.73 to 1.51	1.08	0.75 to 1.56
< 25	64	350	1.08	0.82 to 1.42	1.15	0.87 to 1.52	183	1.13	0.85 to 1.51	1.15	0.86 to 1.53
< 30	99	537	1.09	0.87 to 1.36	1.16	0.93 to 1.45	292	1.10	0.88 to 1.39	1.13	0.90 to 1.43
< 35	148	780	1.08	0.90 to 1.30	1.14	0.95 to 1.37	403	1.18	0.97 to 1.42	1.20	0.99 to 1.45
< 40	195	1053	1.02	0.87 to 1.19	1.08	0.92 to 1.27	536	1.11	0.95 to 1.31	1.14	0.96 to 1.34
≥ 40	177	792	**1.26**	**1.06 to 1.49**	**1.29**	**1.09 to 1.52**	423	**1.27**	**1.06 to 1.51**	**1.30**	**1.09 to 1.55**
Colon, rectum, and anus (C18-C21)											
< 20	2	9	1.47	0.28 to 7.57	1.49	0.29 to 7.69	3	1.75	0.29 to10.60	1.81	0.30 to 11.06
< 25	3	19	0.98	0.27 to 3.48	1.04	0.29 to 3.71	6	1.89	0.46 to 7.80	1.92	0.47 to 7.86
< 30	6	33	1.19	0.48 to 2.96	1.32	0.53 to 3.29	12	1.70	0.63 to 4.55	1.77	0.66 to 4.76
< 35	10	49	1.22	0.60 to 2.48	1.31	0.64 to 2.68	24	1.38	0.66 to 2.89	1.43	0.68 to 3.00
< 40	12	69	1.09	0.57 to 2.07	1.21	0.63 to 2.30	41	0.93	0.48 to 1.78	0.96	0.50 to 1.85
≥ 40	20	94	1.15	0.70 to 1.89	1.17	0.71 to 1.93	37	1.62	0.94 to 2.79	1.63	0.94 to 2.82
Pancreas (C25)											
< 20	0	1					2				
< 25	0	1					5				
< 30	1	12	0.51	0.06 to 4.14	0.55	0.07 to 4.46	5	0.64	0.07 to 5.55	0.62	0.07 to 5.40
< 35	3	19	0.94	0.27 to 3.30	1.00	0.28 to 3.54	7	1.45	0.37 to 5.61	1.47	0.38 to 5.74
< 40	5	25	1.34	0.49 to 3.66	1.45	0.53 to 3.99	12	1.36	0.48 to 3.89	1.40	0.49 to 4.02
≥ 40	6	11	**3.30**	**1.15 to 9.44**	**3.83**	**1.30 to 11.28**	7	**3.08**	**1.01 to 9.36**	**3.40**	**1.09 to 10.63**
Breast (C50)											
< 20	12	50	1.19	0.62 to 2.30	1.34	0.69 to 2.60	23	1.51	0.75 to 3.05	1.60	0.79 to 3.24
< 25	20	80	1.39	0.83 to 2.32	1.52	0.91 to 2.55	43	1.56	0.92 to 2.68	1.57	0.92 to 2.68
< 30	29	106	1.49	0.97 to 2.29	**1.59**	**1.03 to 2.46**	66	1.42	0.92 to 2.21	1.47	0.94 to 2.28
< 35	35	143	1.33	0.91 to 1.96	1.41	0.96 to 2.08	80	1.37	0.92 to 2.04	1.38	0.93 to 2.06

< 40	42	203	1.09	0.77 to 1.53	1.14	0.80 to 1.60	95	1.32	0.92 to 1.90	1.34	0.93 to 1.93
≥ 40	14	74	1.16	0.65 to 2.10	1.17	0.65 to 2.11	38	1.10	0.59 to 2.03	1.09	0.59 to 2.02
Prostate (C61)											
< 20	4	5	**4.61**	**1.08 to19.68**	**5.28**	**1.21 to23.00**	1	**11.0**	**1.24 to99.28**	**11.8**	**1.31 to106.50**
< 25	5	14	2.13	0.71 to 6.34	2.28	0.76 to 6.84	7	2.39	0.74 to 7.67	2.50	0.77 to 8.04
< 30	10	27	2.12	0.98 to 4.58	**2.31**	**1.07 to 5.02**	21	1.62	0.75 to 3.48	1.73	0.80 to 3.73
< 35	15	73	1.10	0.61 to 1.96	1.21	0.67 to 2.17	44	1.13	0.62 to 2.04	1.23	0.67 to 2.23
< 40	24	134	0.96	0.61 to 1.51	1.07	0.68 to 1.68	68	1.14	0.71 to 1.83	1.20	0.75 to 1.93
≥ 40	33	154	1.38	0.93 to 2.06	1.40	0.94 to 2.09	70	1.47	0.97 to 2.24	1.50	0.98 to 2.28
Kidney (C64-C66)											
< 20	2	12	1.10	0.23 to 5.30	1.23	0.26 to 5.97	4	2.45	0.35 to 14.24	2.46	0.38 to 15.74
< 25	2	16	0.77	0.17 to 3.55	0.83	0.18 to 3.84	8	0.82	0.17 to 3.90	0.81	0.17 to 3.81
< 30	2	29	0.43	0.10 to 1.85	0.44	0.10 to 1.89	16	0.41	0.09 to 1.79	0.41	0.09 to 1.79
< 35	6	37	0.97	0.40 to 2.40	1.00	0.41 to 2.47	18	1.07	0.43 to 2.71	1.08	0.43 to 2.72
< 40	8	51	0.83	0.38 to 1.80	0.86	0.40 to 1.87	25	0.96	0.43 to 2.13	0.97	0.44 to 2.15
≥ 40	8	39	1.32	0.60 to 2.91	1.34	0.60 to 2.98	16	1.48	0.63 to 3.46	1.48	0.63 to 3.48
Lymphoid and haematopoietic tissue (LH) (C81-C96, D45-D47)											
< 20	1	15	0.34	0.04 to 2.68	0.37	0.05 to 2.90	14	0.27	0.04 to 2.13	0.29	0.04 to 2.25
< 25	4	21	1.03	0.34 to 3.12	1.11	0.37 to 3.36	23	0.62	0.21 to 1.82	0.63	0.21 to 1.84
< 30	6	43	0.90	0.37 to 2.17	0.96	0.40 to 2.33	28	0.79	0.32 to 1.95	0.79	0.32 to 1.95
< 35	11	62	1.07	0.55 to 2.09	1.14	0.58 to 2.22	34	1.20	0.60 to 2.41	1.20	0.60 to 2.42
< 40	13	81	0.92	0.50 to 1.69	1.00	0.55 to 1.84	41	1.07	0.57 to 2.02	1.08	0.57 to 2.03
≥ 40	24	62	**2.24**	**1.36 to 3.68**	**2.46**	**1.48 to 4.07**	31	**2.34**	**1.37 to 4.00**	**2.67**	**1.55 to 4.60**
Non-Hodgkin´s lymphoma (NHL) (C82-C85)											
< 20	1	5	1.12	0.12 to 10.61	1.24	0.13 to 11.82	5	0.80	0.09 to 7.38	0.83	0.09 to 7.65
< 25	2	9	1.26	0.26 to 6.22	1.39	0.28 to 6.86	9	0.96	0.19 to 4.78	0.96	0.19 to 4.80
< 30	4	17	1.29	0.41 to 4.00	1.41	0.45 to 4.42	12	1.42	0.43 to 4.68	1.41	0.43 to 4.68
< 35	8	24	1.80	0.77 to 4.22	1.93	0.82 to 4.53	13	2.40	0.95 to 6.09	2.40	0.94 to 6.10
< 40	9	29	1.67	0.76 to 3.69	1.86	0.84 to 4.11	13	**2.55**	**1.04 to 6.25**	**2.53**	**1.03 to 6.22**
≥ 40	8	20	**2.76**	**1.15 to 6.63**	**2.98**	**1.23 to 7.20**	7	**3.56**	**1.23 to10.25**	**3.76**	**1.28 to 11.02**

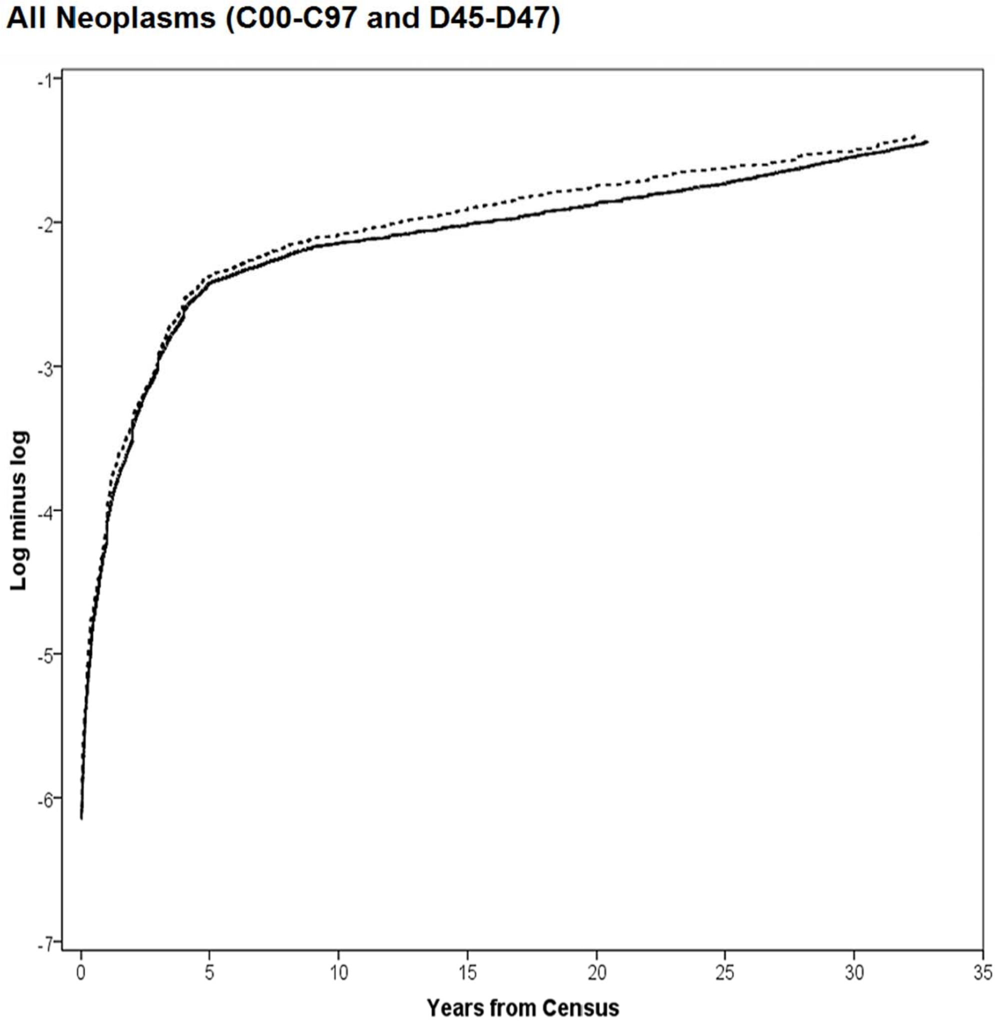
Not included in all cancers											
Basal cell carcinoma of the skin (C44)											
< 20	13	54	1.27	0.68 to 2.37	1.40	0.75 to 2.62	25	1.54	0.78 to 3.02	1.64	0.83 to 3.24
< 25	22	84	1.44	0.88 to 2.33	1.57	0.97 to 2.56	37	**1.89**	**1.11 to 3.22**	**2.07**	**1.21 to 3.54**
< 30	33	116	**1.54**	**1.04 to 2.30**	**1.68**	**1.13 to 2.51**	54	**1.95**	**1.26 to 3.03**	**2.10**	**1.35 to 3.26**
< 35	40	155	1.37	0.97 to 1.95	**1.49**	**1.04 to 2.13**	72	**1.76**	**1.19 to 2.60**	**1.86**	**1.26 to 2.76**
< 40	48	187	1.36	0.98 to 1.89	**1.48**	**1.07 to 2.06**	91	**1.61**	**1.13 to 2.29**	**1.69**	**1.19 to 2.41**
≥ 40	26	170	0.87	0.57 to 1.32	0.87	0.57 to 1.33	63	1.26	0.79 to 1.99	1.28	0.80 to 2.03

Table O. Number of individuals, number of male breast cancer cases, number of individuals with and without mutation of the BRCA2 gene, the prevalence of those with, and without the mutation according to Thorlacius et al. [31], and predictive values for breast cancer among females according to the method of Axelson and Steenland [29], and using the relative risk for breast cancer among female according to Thorlacius et al. [32], in the geothermal area in comparison with warm and cold reference areas, and the combined capital area and Reykjanes.

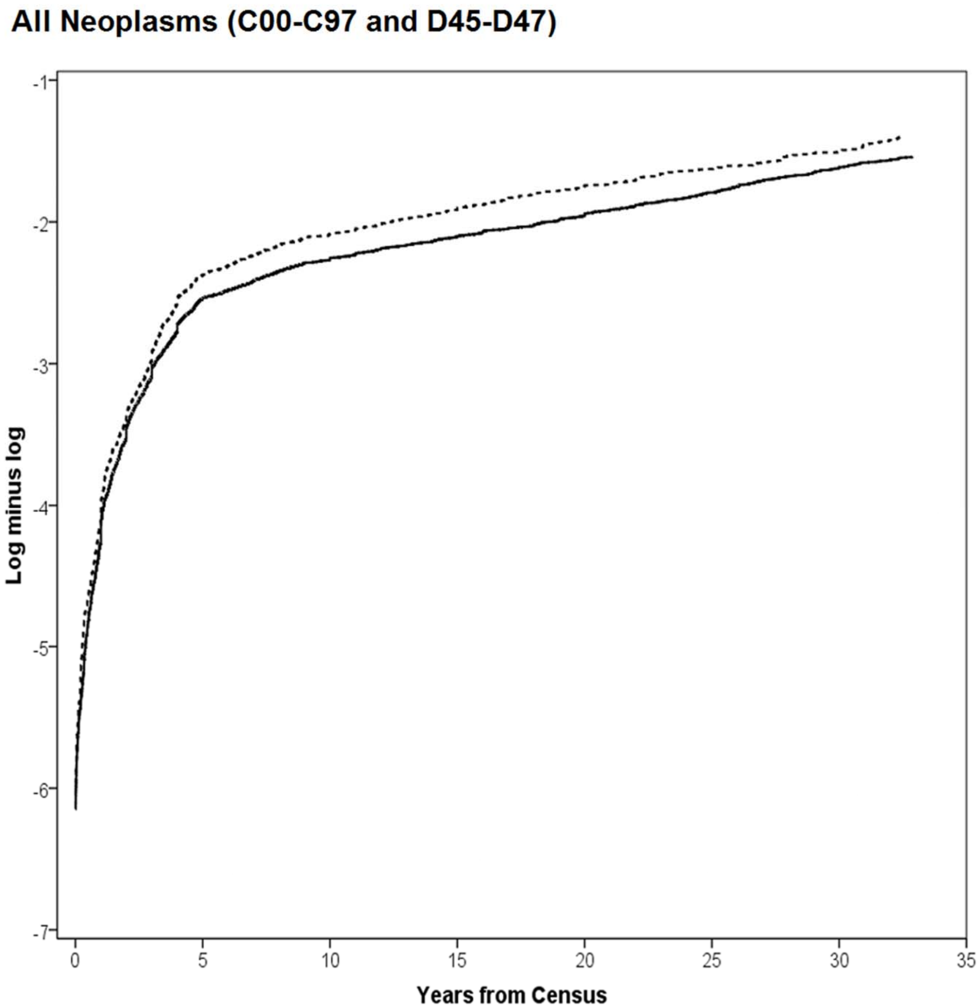
			The mutation of BRCA2 gene					
Areas	No of individuals	No male breast cancer	Estimated number with BRCA2	Estimated number without BRCA2	Estimated prevalence with BRCA2	Estimated prevalence without BRCA2	Risk of female breast cancer	Predictive values (risk ratio)
Geothermal heating area	7511	3	87	7424	1.16	98.84	106.97	
Warm reference area	44 864	9	262	44 602	0.58	99.42	103.50	1.03
Cold reference area	22 431	5	145	22 286	0.65	99.35	103.89	1.03
Reykjavik capital area and Reykjanes	109 308	21	610	108 698	0.56	99.44	103.35	1.03
Census	184 114	38	1105	183 009	0.60	99.40	103.60	NC[1]

[1] NC, not compared.

S1 Fig The log(-log(survival)) versus log(time) curves for exposed group (dashed line) and warm reference group (black line).



S2 Fig The log(-log(survival)) versus log(time) curves for exposed group (dashed line) and cold reference group (black line).



Study approvals

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Reykjavík, 6. september 2010
Tilvísun: 2010060524ÞPJ/--

Heimild samkvæmt 3. mgr. 15. gr. laga nr. 74/1997 og 8. mgr. 1. gr. 8. gr. laga nr. 41/2007, veitt í samræmi við 1. og 7. tl. 1. mgr. 4. gr. reglna 712/2008 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga.

I.
Umsókn

Persónuvernd vísar til fyrri samskipta af tilefni umsóknar, dags. 28. júní 2010, frá Vilhjálmi Rafnssyni, prófessor, f.h. Miðstöðvar í Lýðheilsuvísindum, Aðalbjörgu Kristbjörnsdóttur, MPH-nema, Laufeyju Tryggvadóttur, Framkvæmdastjóra Krabbameinsskrár, Unni Önnu Valdimarsdóttur, dósent í faraldsfræði, og Hólmfríði Kolbrúnu Gunnarsdóttur, gestaprófessor hjá Miðstöð í lýðheilsuvísindum við HÍ. Í umsókninni er farið fram á heimild til vinnslu persónuupplýsinga vegna rannsóknarinnar „Byggingarefni húsa og áhætta á krabbameini: Lýðgrunduð hóprannsókn". Fram kemur að rannsóknin er þáttur í meistaraverkefni Aðalbjargar Kristbjörnsdóttur við Miðstöð í lýðheilsuvísindum HÍ. Tilgangur rannsóknarinnar er sagður sá að rannsaka hvort íbúum húsa, sem byggð eru úr holsteini, er hættara við að fá krabbamein samanborið við þá sem búa í steyptum húsum og timburhúsum. Óskað er leyfis til að mega samkeyra manntalsgögn frá 1981 við Krabbameinsskrá. Í umsókn er þessu svo lýst:

„Þetta er aftursýn hóprannsókn sem tekur til húsa á Íslandi sem skráð hafa verið hjá Fasteignaskrá Íslands til ársins 1981 og allra einstaklinga, sem skráðir voru sem íbúar tiltekinna húsa í manntalinu á Íslandi

sem framkvæmt var 31. júlí 1981.
Rannsóknin byggir á gögnum sem fengin verða frá Fasteignaskrá Íslands, Hagstofu Íslands og úr Kabbameinsskrá og eru hlutaðeigandi aðilar upplýstir um fyrirhugaða rannsókn samanber fylgigögn.

Upplýsinga sem aflað verður frá Fasteignaskrá eru staðsetning húsa, byggingarár, byggingargerð og byggingarefni. Gögn frá Hagstofu Íslands, manntal 1981, eru: kyn, kennitala, heimilisfang, póstnúmer, sveitarfélagsnúmer, staða, menntun, dánardægur, dánarmein og hvort einstaklingar hafi flutt af landi brott og þá hvenær. Frá Kabbameinsskrá verða fengnar upplýsingar um greind krabbamein.
Afrakstur samkeyrslunnar verður á ópersónugreinanlegu formi og eftir að öllum gögnum hefur verið safnað saman til rannsóknarinnar og verða kennitölur dulkóðaðar og lykill geymdur hjá gagnastjóra Miðstöðvar í lýðheilsuvísindum. Er þetta gert til að fyrirbyggja að óviðkomandi aðilar komist í gögnin meðan á vinnslu stendur, og unnt verði að gera leiðréttingar ef upp koma villur í gögnunum.

Greiningarlykill og grunngögn verða geymd hjá Krabbameinsskrá í fimm ár eftir að rannsókn lýkur.
Eingöngu framkvæmdaraðilar rannsóknarinnar munu hafa aðgang að rannsóknargögnum og munu þeir ekki láta gögn í annarra hendur. "

Í umsókninni segir ennfremur:

„Sameining upplýsinga verður gerð með samkeyrslum og munu þær fara fram með þeim hætti að tryggt sé að upplýsingar af einni skrá geti ekki orðið eftir hjá öðrum skrárhaldara. Þetta öryggisatriði verður tryggt með því að samkeyrsla fari fram á frístandandi tölvu (tölvu sem ekki er tengd við net, hvorki innanhúsnet eða internetið) sem gögnin eru færð inn á og þeim eytt þaðan með öruggum hætti að samkeyrslu lokinni. Skrár verða fluttar milli Fasteignaskrár, Hagstofu, Krabbameinsfélags og Miðstöðvar í lýðheilsuvísindum á geisladiski og engin gögn verða flutt yfir netið. Samkeyrslan fer fram í tveim áföngum, fyrst eru gögn Hagstofu samkeyrð við gögn úr Fasteignaskrá og sú tenging gerð á heimilisföngum. Síðan eru sameinuð gögn Hagstofu og Fasteignaskrár samkeyrð við gögn Krabbameinsskrá á dulkóðuðum kennitölum.
Upphafsgögn rannsóknarinnar eru hjá Hagstofu Íslands, úr manntalinu frá 1981. Einstaklingar úr manntalinu, eru valdir í rannsóknina og þeim fylgt eftir. Lýkur eftirfylgni á dánardægri þeirra, við brottflutning af landinu eða þegar rannsókninni lýkur 31. júlí 2009. Þegar gögn Hagstofu hafa verið að fullu unnin eru þau samkeyrð við gögn Fasteignaskrár, byggt á heimilisföngum. Frá Fasteignaskrá eru fengnar upplýsingar um hús sem byggð hafa verið til ársins 1981 og þau flokkuð niður í holsteinshús, steypt hús og timburhús. Valdir eru einstaklingar sem búa í holsteinshúsum sem útsettir og einstaklingar sem búa í öðrum húsum eru hafðir til samanburðar.
Þegar gögn Fasteignaskrár og Hagstofu liggja fyrir eru þau samkeyrð á dulkóðuðum kennitölum við Krabbameinsskrá. Frá Kabbameinsskrá eru fengin gögn um krabbamein hjá einsklingum og hvaða krabbameinsgerðir um er að ræða. [...]
Þegar samkeyrslu er lokið eru kennitölur dulkóðaðar. Dulkóðunarlykill og grunngögn verða geymd hjá gagnagrunnstjóra Miðstöðvar í lýðheilsuvísindum.
Gögn rannsóknarinnar eru alltaf á rafrænu formi og lokavinnsla þeirra í rannsókninni verður unnin á Rannsóknarstofu í heilbrigðisfræði... "

Samkvæmt umsókn verða gögn auðkennd með dulkóðuðum kennitölum, en til verða dulkóðunarlyklar. Um varðveislu gagna segir:

„Öll gögn rannsóknarinnar eru á tölvutæku formi. Tölvan sem þau eru geymd í verður einungis hægt að opna með lykilorði og hún verður staðsett á lokuðu svæði þar sem ábyrgðarmaður, gagnastjóri og samstarfsmenn hafa einir aðgang að.
Gögn verða varðveitt hjá Karbbameinsskrá og fimm árum eftir að rannsókn lýkur verður öllum gögnum eytt. "

Persónuvernd hefur borist afrit af bréfi Krabbameinsskrár til Vilhjálms Rafnssonar, dags. 14. júní 2010, þar sem fallist er á að veita aðgang að gögnum vegna rannsóknarinnar.

II.
Leyfisskyld og tilkynningarskyld vinnsla
Ábyrgðaraðili og leyfishafi

Samkvæmt 7. tölul. 1. mgr. 7. gr. reglna Persónuverndar nr. 712/2008 er miðlun viðkvæmra persónuupplýsinga í þágu vísindarannsóknar háð leyfi Persónuverndar, enda standi ábyrgðaraðili þeirra upplýsinga sem miðlað er ekki að rannsókninni. Samkvæmt 1. tölul. 1. mgr. 7. gr. sömu reglna er samkeyrsla skráa með viðkvæmum persónuupplýsingum auk þess háð leyfi Persónuverndar, nema þegar einvörðungu eru samkeyrðar upplýsingar úr þjóðskrá um nöfn, kennitölur, fyrirtækjanúmer, heimilisföng, aðsetur og póstnúmer; aðeins eru samkeyrðar skrár sama ábyrgðaraðila, þó að undanskildum miðlægum skrám sem innihalda viðkvæmar persónuupplýsingar; eða samkeyrslan byggist á skriflegu samþykki eða lagafyrirmælum. Engin af þessum undantekningum á við um umrædda samkeyrslu upplýsinga um dánarmein frá Hagstofu Íslands aðili við Krabbameinsskrá Landlæknis, m.a. þar sem um er að ræða miðlægar skrár með viðkvæmum persónuupplýsingum. Þarf því leyfi með stoð í 1. tölul. 1. mgr. 7. gr.

Krabbameinsskrá er varðveitt hjá Krabbameinsfélagi Íslands en Landlæknisembættið skipuleggur skrána og er ábyrgðarmaður hennar, sbr. 4. tölul. 2. mgr. og 4. mgr. 8. gr. laga nr. 41/2007 um landlækni. Samkvæmt 8. mgr. sömu greinar, sbr. 3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga, þarf leyfi Persónuverndar til aðgangs að þeirri skrá.

III.
Leyfisskilmálar

Persónuvernd hefur fjallað um umsókn Vilhjálms Rafnssonar, prófessors, f.h. Miðstöðvar í Lýðheilsuvísindum, Aðalbjargar Kristbjörnsdóttur, MPH-nema, Laufeyjar Tryggvadóttur, Framkvæmdastjóra Krabbameinsskrár, Unnar Önnu Valdimarsdóttur, dósents í faraldsfræði, og Hólmfríðar Kolbrúnar Gunnarsdóttur, gestaprófessors hjá Miðstöð í lýðheilsuvísindum við HÍ, dags. 28. júní 2010, í ljósi 1. og 7. tölul. 1. mgr. 7. gr. reglna nr. 712/2008 um tilkynningarskylda og leyfisskylda vinnslu persónuupplýsinga, sbr. 33. gr. laga nr. 77/2000 um persónuvernd og meðferð persónuupplýsinga, og 8. mgr. 8. gr., sbr. 4. tölul. 2. mgr. 8. gr. laga nr. 41/2007 um landlækni, sbr. 3. mgr. 15. gr. laga nr. 74/1997 um réttindi sjúklinga. Með vísan til þessara ákvæða, sem og m.a. að virtum ákvæðum 29., 33. og 34. gr. í formálsorðum persónuverndartilskipunarinnar nr. 95/46/EB, ákvæði 9. tölul. 1. mgr. 9. gr. laga nr. 77/2000, hefur stofnunin ákveðið að veita umbeðið leyfi til vinnslu persónuupplýsinga vegna rannsóknarinnar „Byggingarefni húsa og áhætta á krabbameini: Lýðgrunduð hóprannsókn".

Leyfi þetta gildir til **1. september 2015** og er bundið eftirfarandi skilyrðum:

1. Ábyrgðaraðilar að vinnslu persónuupplýsinga

Vilhjálmur Rafnsson, prófessor, f.h. Miðstöðvar í Lýðheilsuvísindum, Aðalbjörg Kristbjörnsdóttir, MPH-nemi, Laufey Tryggvadóttir, Framkvæmdastjóri Krabbameinsskrár, Unnur Anna Valdimarsdóttir, dósents í faraldsfræði, og Hólmfríður Kolbrún Gunnarsdóttir, gestaprófessor hjá Miðstöð í lýðheilsuvísindum við HÍ (hér eftir sameiginlega nefnd „leyfishafar") teljast vera ábyrgðaraðilar vinnslunnar í skilningi 4. tölul. 2. gr. laga nr. 77/2000. Fer Vilhjálmur Rafnsson með allt fyrirsvar gagnvart Persónuvernd um alla þætti er varða þetta leyfi, þ. á m. álitaefni er upp kunna að rísa um það hvort vinnsla persónuupplýsinga hafi verið í samræmi við lög, reglur og ákvæði þessa leyfis.

2. Lögmæt vinnsla persónuupplýsinga og þagnarskylda

a. Leyfishafi ber ábyrgð á því að vinnsla persónuupplýsinga vegna rannsóknarinnar fullnægi ávallt kröfum 1. mgr. 7. gr. laga nr. 77/2000.

b. Farið skal með upplýsingar, sem skráðar eru vegna rannsóknarinnar, í samræmi við lög nr. 77/2000, lög nr. 55/2009 um sjúkraskrár, lög nr. 74/1997 um réttindi sjúklinga og læknalög nr. 53/1988. Hvílir þagnarskylda á leyfishafa og öðrum þeim sem koma að rannsókninni um heilsufarsupplýsingar sem unnið er með, sbr. 15. gr. laga nr. 53/1988. Þagnarskylda helst þótt látið sé af störfum við rannsóknina.

c. Taki háskólanemar eða aðrir, sem ekki teljast til löggiltra heilbrigðisstétta, þátt í framkvæmd rannsóknarinnar skulu þeir undirrita sérstaka þagnarskylduyfirlýsingu, þar sem þeir m.a. ábyrgjast að tilkynna leyfishafa ef í rannsóknargögnum eru viðkvæmar persónuupplýsingar um þá sem eru eða hafa verið maki viðkomandi, skyldir eða mægðir honum í beinan legg eða að öðrum lið til hliðar eða tengdir honum með sama hætti vegna ættleiðingar. Er viðkomandi þá óheimilt að kynna sér gögn um þá einstaklinga. Leyfishafa eða fulltrúa hans ber að votta rétta undirskrift hlutaðeigandi og dagsetningu slíkrar yfirlýsingar og koma henni til Persónuverndar innan tveggja vikna frá útgáfu leyfis þessa eða frá því að viðkomandi hefur störf við rannsóknina. Þagnarskyldan er byggð á 3. mgr. 35. gr. laga nr. 77/2000. Á heimasíðu Persónuverndar er að finna staðlað eyðublað fyrir þagnarskylduyfirlýsingu. Ef þagnarskylduyfirlýsingum er ekki skilað innan tilskilins frests getur Persónuvernd afturkallað leyfi þetta.

d. Leyfi þetta heimilar einvörðungu að safnað verði úr sjúkraskrám þeim heilsufarsupplýsingum sem gildi hafa fyrir rannsókn leyfishafa og samrýmast markmiðum hennar. Hafi sjúkraskrárupplýsingar í sjúkraskrá verið merktar sérstaklega viðkvæmar í samræmi við 2. mgr. 13. gr. laga nr. 55/2009 heimilar leyfi þetta eingöngu að slíkum upplýsingum verði safnað hafi þær augljóst vægi fyrir gæði rannsóknar og niðurstöður.

e. Leyfi þetta heimilar ekki rannsakendum aðgang að sjúkraskrárupplýsingum hafi viðkomandi sjúklingur eða umboðsmaður hans lagt bann við því að rannsakandi, eða annars tiltekinn aðili sem starfar á hans vegum, hafi slíkan aðgang að sjúkraskrá viðkomandi skv. 4. mgr. 13. gr. sjúkraskrárlaga nr. 55/2009.

3. Vinnuferli – Dulkóðun

a. Öll rannsóknargögn skulu varðveitt á dulkóðuðum kennitölum eingöngu.

b. Þær upplýsingar, sem heimilt er að samkeyra, eru annars vegar upplýsingar frá Hagstofu, sbr. kafla I. í leyfi þessu og hins vegar tilgreindar upplýsingar úr Kabbameinsskrá.

c. Umsjónarmaður Kabbameinsskrár skal dulkóða upplýsingar frá Hagstofu og úr Kabbameinsskrá með sama hætti. Greiningarlykill skal varðveittur á öruggum stað og aðeins vera aðgengilegur umsjónarmanninum.

d. Upplýsingar frá Hagstofu, sem sendar eru til Landlæknisembættisins, skulu sendar því með öruggum hætti, s.s. á geisladiski sem komið er til skila í innsigluðu umslagi.

e. Þegar þær heilbrigðisupplýsingar, sem leyfi þetta tekur til, hafa verið skráðar í rannsóknargögn, og eftir atvikum verið staðreynt að þær séu réttar, og gögnin að öðru leyti verið fullgerð, skal tryggja að þar liggi ekki fyrir auðkenning á því frá hvaða einstaklingi upplýsingarnar stafa, þ.e. með því að eyða greiningarlykli. Ber landlæknir ábyrgð á því að senda Persónuvernd tilkynningu um eyðinguna.

4. Öryggi við vinnslu persónuupplýsinga

Leyfishafa ber að gera viðeigandi tæknilegar og skipulagslegar öryggisráðstafanir til að vernda persónuupplýsingar gegn óleyfilegum aðgangi í samræmi við 11. og 12. gr. laga nr. 77/2000. Þar er m.a. áskilið að:

a. beita skuli ráðstöfunum sem tryggja nægilegt öryggi miðað við áhættu af vinnslunni og eðli þeirra gagna sem verja á, með hliðsjón af nýjustu tækni og kostnaði við framkvæmd þeirra, og

b. tryggja skuli að áhættumat og öryggisráðstafanir við vinnslu persónuupplýsinga séu í samræmi við lög, reglur og fyrirmæli Persónuverndar um hvernig tryggja skal öryggi upplýsinga, þ.m.t. þá staðla sem hún ákveður að skuli fylgt.

Leyfishafi ber ábyrgð á því að hver sá er starfar í umboði hans og hefur aðgang að persónuupplýsingum vinni aðeins með þær í samræmi við skýr fyrirmæli sem hann gefur og að því marki að falli innan skilyrða leyfis þessa, nema lög mæli fyrir á annan veg, sbr. 3. mgr. 13. gr. laga nr. 77/2000.

5. Varðveisla og eyðing gagna

a. Ávallt skal tryggt að rannsóknargögn séu varðveitt á tryggum stað og aðeins þar sem lögum samkvæmt er heimilt að varðveita þau.

b. Að lokinni þeirri rannsókn, sem leyfi þetta tekur til, þó eigi síðar en við lok gildistíma leyfisins hinn 1. september 2015, ber að eyða öllum rannsóknargögnum.

6. Almennir skilmálar

a. Leyfishafi ber ábyrgð á að farið sé með öll persónuauðkennd gögn sem sjúkragögn í samræmi við lög, reglur og ákvæði þessa leyfis.

b. Leyfishafi skal ábyrgjast að engir aðrir en hann fái í hendur persónugreinanleg gögn sem sérstaklega verður aflað í þágu þessarar rannsóknar.

c. Óski leyfishafi þess að hætta rannsókn ber honum að leggja þetta leyfi inn til Persónuverndar á skriflegan og sannanlegan hátt. Skal þá tilgreina hvort þeim persónuupplýsingum, sem unnar voru á grundvelli þessa leyfis, hafi verið eytt. Að öðrum kosti úrskurðar Persónuvernd um hvort persónuupplýsingunum skuli eytt eða þær varðveittar með ákveðnum skilyrðum.

d. Leyfishafa ber að veita Persónuvernd, starfsmönnum og tilsjónarmönnum hennar allar umbeðnar upplýsingar um vinnslu persónuupplýsinga sé eftir því leitað í þágu eftirlits. Brot á ákvæði þessu getur varðað afturköllun á leyfinu.

e. Persónuvernd getur látið gera úttekt á því hvort leyfishafi fullnægi skilyrðum laga nr. 77/2000 og reglna sem settar eru samkvæmt þeim eða einstökum fyrirmælum. Getur Persónuvernd ákveðið að hann skuli greiða þann kostnað sem af því hlýst. Persónuvernd getur einnig ákveðið að leyfishafi greiði kostnað við úttekt á starfsemi, við undirbúning útgáfu vinnsluleyfis og annarrar afgreiðslu. Persónuvernd skal þá gæta þess að sá sérfræðingur, sem framkvæmir umrædda úttekt, undirriti yfirlýsingu um að hann lofi að gæta þagmælsku um það sem hann fær vitneskju um í starfsemi sinni og leynt ber að fara eftir lögum eða eðli máls. Brot á slíkri þagnarskyldu varðar refsingu samkvæmt 136. gr. almennra hegningarlaga. Þagnarskyldan helst þótt látið sé af starfi.

f. Leyfi þetta er háð því skilyrði að einungis verði safnað þeim upplýsingum sem *nauðsynlegar* eru vegna rannsóknarinnar.

Virðingarfyllst

Sigrún Jóhannesdóttir

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Reykjavík 7. desember 2010
Tilv.: VSNb2010060005/03.1

Efni: Varðar: 10-083-S1 Byggingarefni húsa og áhætta á krabbameini: Lýðgrunduð hóprannsókn.

Vísindasiðanefnd þakkar svarbréf þitt, vegna áðursendra athugasemda við ofangreinda rannsóknaráætlun sbr. bréf nefndarinnar dags. 22.06.2010. Í bréfinu koma fram svör og skýringar til samræmis við athugasemdir Vísindasiðanefndar og því fylgdu endurbætt umsókn, leyfi Persónuverndar og frá Þjóðskrá Íslands.

Fjallað hefur verið um svarbréf þitt og önnur innsend gögn og eru þau talin fullnægjandi.

Rannsóknaráætlunin er endanlega samþykkt af Vísindasiðanefnd.

Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Jafnframt fer Vísindasiðanefnd fram á að fá send afrit af, eða tilvísun í, birtar greinar um rannsóknina. Rannsakendur eru minntir á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju,
f.h. Vísindasiðanefndar,

dr. med., Björn Rúnar Lúðvíksson, læknir, formaður