

# Cancer Experience of Men Exposed to Inhalation of Chemicals or to Combustion Products

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This article identifies instances of excess cancer in men who were exposed to the inhalation of chemicals or combustion products. The survey covers 13 occupations and 17 cancer sites. It is based on a detailed statistical analysis of the relevant subseries from an overall series of approximately 17,000 patients admitted to Roswell Park Memorial Institute in Buffalo, New York, between 1956 and 1965. This analysis used the Woolf-Haldane and Cochran statistical tests for the calculation of the relative risk and related probabilities at each cancer site for each suspect occupation. Where necessary, this analysis takes into account other collateral variables, such as age at time of diagnosis, smoking habits and duration of employment.

This general survey covers a large class of occupations and various sites of cancers, and it is, in some respects, the first of its kind. In other respects, however, it has features in common with previous types of occupational studies on cancers and hence shows both the advantages and the disadvantages of such studies.

This investigation is basically a retrospective or case-control study. It looks at a population of patients with specific diagnosis of cancer or of non-neoplastic diseases and goes back to study their occupational history. The advantage of this case-control study is that it is not necessary to wait for a long time between exposure to a noxious agent and the occurrence of specific cancers. Moreover, it avoids the most common pitfalls of many retrospective studies by using a non-neoplastic series in the calculation of the relative risk. The non-neoplastic series consists of various diseases. However, all patients were referred to the institute because they were suspected of having cancer. Sometimes after the epidemiological interview it was established that they did not have neoplastic disease.

This investigation is different from the usual occupational studies which start from a group of individuals exposed to risk in the past, such as workers in a chemical plant, and then tries to follow up this person with cancer registries or with death certificates. This research is also different from prospective studies, i.e.

follow-up of a cohort employed in a specific industry, till some members of the cohort develop the disease of interest, i.e. special cancers.

The usual studies of workers (prospective or historical prospective studies) have more details on the occupational exposure but may lack detail on other environmental variables such as cigarette smoking and/or diagnosis. The main weakness of the usual occupational studies is that there may not be enough cases of cancer at specific sites to allow for statistical analysis, whereas this hospital survey has an advantage in this respect.

It also has an advantage over most previous retrospective studies based on hospital records because the data were collected systematically for epidemiological research and are not limited to cancers at a single site.

While the Roswell Park sample is not strictly population-based, RPMI serves Western New York and is the only cancer hospital in this area. This screening over a broad class of cancers and occupations has been conceived as a preliminary analysis which can produce interesting etiologic leads which might be pursued further by other types of studies.

## Materials and Methods

This investigation used the epidemiology schedules administered to patients admitted to Roswell Park Memorial Institute from 1956 till 1965. The information obtained was very extensive and included the patient lifetime occupational history, sex and age at diagnosis, the specific diagnosis by cancer site, country of birth, education level and a detailed smoking history.

The occupational history was used extensively with the smoking habits of the patient. Each job was classified by industry and by occupation. However, the double classification was used only if the occupation was not specific enough, such as in the operatives series. All the occupations which were screened belonged either to the metal industry, to dust products, to the chemical and combustion series. Here, only a subseries of these occupations is presented, e.g. those related either to the inhalation of combustion products or to the inhalation of chemicals. All oc-

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Table 1. — Relative Risks Standardized for Age and Related Probabilities for Men in Selected Occupations (Ever Exposed and Exposed 5 Years or More to the Occupation With a Sample Size of 5 Cancer Cases or More).

Cancer Diagnosis	Age At Diagnosis	No. Of Cases	Ever Exposed		No. Of Cases	Exposed 5 Years or More	
			Relative Risk	Probability		Relative Risk	Probability
<b>Barbers</b>							
Larynx	< 60	1	1.133	> .05	1	0.964	> .05
	60+	9	3.448	< .05	7	3.208	< .05
	All	10	2.828	< .05	8	2.493	> .05
Bladder	< 60	1	1.762	> .05	1	1.929	> .05
	60+	4	1.434	> .05	4	1.737	> .05
	All	5	1.490	> .05	5	1.772	> .05
<b>Operatives in Chemical Industry</b>							
Larynx	< 60	6	2.379	> .05	6	6.750	< .05
	60+	3	1.478	> .05	3	2.200	> .05
	All	9	1.905	> .05	9	3.862	< .05
Lung	< 60	4	0.444	> .05	3	0.818	> .05
	60+	10	2.506	> .05	7	2.310	> .05
	All	14	1.123	> .05	10	1.508	> .05
Buccal Cavity & Pharynx	< 60	5	0.555	> .05	3	0.844	> .05
	60+	7	2.041	> .05	6	2.400	> .05
	All	12	0.994	> .05	9	1.562	> .05
Stomach	< 60	4	11.100	< .05	3	27.000	< .05
	60+	2	2.381	> .05	2	2.933	> .05
	All	6	4.250	< .05	5	5.885	< .05
<b>Operatives in Leather Industry</b>							
Larynx	< 60	1	0.881	> .05	†	†	†
	60+	6	6.897	< .05	6	22.000	< .05
	All	7	3.633	< .05	6	6.856 ‡	< .05 ‡
Buccal Cavity & Pharynx	< 60	6	1.480	> .05	3	1.012	> .05
	60+	12	8.163	< .05	9	18.000	< .05
	All	18	3.378	< .05	12	3.772	< .05
Bladder	< 60	2	2.741	> .05	1	2.700	> .05
	60+	9	9.677	< .05	7	24.316	< .05
	All	11	6.773	< .05	8	12.935	< .05
<b>Painters</b>							
Lung	< 60	21	2.119	< .05	14	1.762	> .05
	60+	21	1.417	> .05	15	1.031	> .05
	All	42	1.708	< .05	29	1.306	> .05
Esophagus	< 60	2	2.018	> .05	1	1.038	> .05
	60+	5	3.846	< .05	5	6.875	< .05
	All	7	2.994	< .05	6	3.230	< .05
Stomach	< 60	5	12.614	< .05	4	16.615	< .05
	60+	3	0.962	> .05	2	0.611	> .05
	All	8	2.384	> .05	6	1.859	> .05
Prostate	< 60	1	1.261	> .05	1	1.385	> .05
	60+	8	2.051	> .05	5	1.250	> .05
	All	9	1.905	> .05	6	1.271	> .05
<b>Print Workers</b>							
Lung	< 60	4	2.220	> .05	—	—	—
	60+	3	1.053	> .05	—	—	—
	All	7	1.510	> .05	—	—	—
Buccal Cavity & Pharynx	< 60	5	2.775	> .05	4	2.250	> .05
	60+	6	2.449	> .05	6	2.400	> .05
	All	11	2.585	< .05	10	2.332	> .05
<b>Bakers</b>							
Lymphomas	< 60	3	2.030	> .05	—	—	—
	60+	3	2.041	> .05	—	—	—
	All	6	2.026	> .05	—	—	—

\* = Probability value of borderline significance

† = Number of cases was zero

‡ = Overall relative risk and probability are less reliable

Table 2. — Relative Risks Standardized for Age and Related Probabilities for Men in Selected Occupations (Ever Exposed and Exposed 5 Years or More to the Occupation With a Sample Size of 5 Cancer Cases or More).

Cancer Diagnosis	Age At Diagnosis	No. Of Cases	Ever Exposed		No. Of Cases	Exposed 5 Years or More	
			Relative Risk	Probability		Relative Risk	Probability
<b>Bus Drivers, Taxicab Drivers and Truck Drivers</b>							
Buccal Cavity & Pharynx	< 60	49	1.037	>.05	39	0.982	>.05
	60+	40	2.268	<.05	29	1.933	*.05
	All	89	1.436	>.05	68	1.325	>.05
Stomach	< 60	5	2.509	>.05	2	1.612	>.05
	60+	6	1.389	>.05	3	0.733	>.05
	All	11	1.605	>.05	5	0.885	>.05
Pancreas	< 60	1	1.028	>.05	—	—	—
	60+	4	2.778	>.05	—	—	—
	All	5	2.222	>.05	—	—	—
Kidney	< 60	6	1.233	>.05	5	2.015	>.05
	60+	1	1.389	>.05	1	1.100	>.05
	All	7	1.251	>.05	6	1.615	>.05
<b>Deliverymen and Routemen</b>							
Bladder	< 60	4	2.596	>.05	—	—	—
	60+	4	0.717	>.05	—	—	—
	All	8	1.126	>.05	—	—	—
Skin (Other)	< 60	7	1.636	>.05	7	3.150	*.05
	60+	4	0.494	>.05	2	0.344	>.05
	All	11	0.890	>.05	9	1.137	>.05
<b>Kitchen Workers, Except Private Household</b>							
Buccal Cavity & Pharynx	< 60	4	1.110	>.05	—	—	—
	60+	5	2.551	>.05	—	—	—
	All	9	1.629	>.05	—	—	—
<b>Locomotive Engineers and Firemen</b>							
Buccal Cavity & Pharynx	< 60	4	0.888	>.05	4	1.350	>.05
	60+	14	2.198	>.05	13	2.364	>.05
	All	18	1.635	>.05	17	1.967	>.05
Bladder	< 60	1	1.233	>.05	1	2.700	>.05
	60+	7	1.737	>.05	6	1.895	>.05
	All	8	1.647	>.05	7	1.981	>.05
Lymphomas	< 60	2	0.542	>.05	2	1.350	>.05
	60+	6	2.198	>.05	6	2.769	>.05
	All	8	1.227	>.05	8	2.132	>.05
<b>Mechanics and Repairmen</b>							
Nose	< 60	2	1.337	>.05	2	2.250	>.05
	60+	7	2.121	>.05	6	2.106	>.05
	All	9	1.888	>.05	8	2.134	>.05
Pancreas	< 60	3	4.012	>.05	3	3.375	>.05
	60+	4	1.515	>.05	2	0.936	>.05
	All	7	2.034	>.05	5	1.590	>.05
Prostate	< 60	6	2.006	>.05	4	1.500	>.05
	60+	21	2.121	<.05	12	1.532	>.05
	All	27	2.095	<.05	16	1.523	>.05

- \* = Probability value of borderline significance
- † = Number of cases was zero
- ‡ = Overall relative risk and probability are less reliable

occupations discussed are classified as skilled or semi-skilled with the only exception of barbers and kitchen workers, classified as service workers by the "Standard Industrial Classification Manual".

The occupations related to the inhalation of combustion products are: (1) bakers, (2) bus drivers, (3) deliverymen and routemen, (4) kitchen workers, (5) locomotive engineers and firemen, (6) mechanics and repairmen, (7) stationary engineers and (8) stationary firemen.

The occupations related to the inhalation of chemicals are: (1) barbers, (2) chemical operatives and laborers, (3) leather operatives, (4) painters, (5) printers, and (6) rubber operatives.

The interviewer did not know whether the patient would have been classified as having cancer, or a benign tumor or a non-neoplastic disease. Such an interview avoided biases which might have arisen, for example, in relation to the smoking habits of the patient if the interviewer had already known the specific diagnosis. All the patients were sent to Roswell Park Memorial Institute because they were suspected of having cancer; however, it turned out that approximately 24% of the entire hospital series had a non-neoplastic disease.

The total sample size in the hospital population consisted of 11,591 white men including the cancer cases and the non-

neoplastic controls. Each patient was counted as many times as the number of different occupations where he worked. The total sample size of white males after counting each different occupation in each patient amounted to 17,714 cancer cases and non-neoplastic controls.

The cancer diagnosis was site specific and did not include a histologic subgrouping. These analyses included only those anatomical sites comprising at least 1% of the hospital population. The cancer sites were the mouth and pharynx, esophagus, stomach, pancreas, colon and rectum combined, nose, larynx, lungs, kidney, bladder, testes, prostate, skin, skin melanoma, myeloma, malignant lymphomas and leukemias.

The control series was made of all the non-neoplastic disease, combined. These included a rather large number of diseases, i.e. diseases of the arteries, respiratory and digestive systems, male genital organs, skin, bones, senility, and diseases due to external causes (traumas). There are advantages in combining all non-neoplastic diseases, namely that of obtaining a relatively large sample size in the controls and that of reducing the possible effect that certain occupations may have had on specific non-neoplastic disease, which would lead to an underestimation of the relative risk.

The clerical series was chosen as an occupation with no exposure to known hazards. There are several reasons for this choice. First of all, the type of work performed by clerks is believed to be relatively free from exposure to carcinogens. Second, when the clerks were compared to the combined series of all other occupations, they seldom showed either an increased or a decreased frequency for any specific cancer.

The cases and the controls were subdivided by the age at time of diagnosis. Age 60 was chosen as the dividing age because it subdivided the sample size of the non-neoplastic series in almost two equal parts. Detailed information was available on the smoking history, i.e. a case or control was classified as a non-smoker or as a smoker; if a smoker, it was specified whether he was a light cigarette smoker (up to 20 cigarettes a day), a heavy cigarette smoker (more than one pack a day), or a cigar and/or pipe smoker.

This occupational screening was carried out both for the ever exposed to a suspect occupation and for those employed in a specific occupation for at least five years. This subdivision is of use in seeing whether a longer exposure to a dangerous occupation might have increased the relative risks.

Smoking and age standardizations were performed simultaneously within each occupational subgroup. In specific occupations, however, smoking and age adjustments were performed independently to avoid empty cells. The smoking standardization was performed in the overall exposure and in the "five or more years of exposure" groups. As a general rule, cancers of the mouth, pharynx, larynx, lung and bladder were considered to be occupation related if the relative risks were still significant after both the age and smoking adjustments.

The Cochran and Woolf-Haldane tests<sup>1 2 3</sup> were used throughout to evaluate the statistical significance of age-adjusted and/or smoking adjusted comparisons of percentage differences between cases and controls, both of them either belonging to a suspect occupation or to the nonsuspect one.

## Overall Results

The occupations of both the chemical and combustion subgroups were analyzed by combining them together (two main subgroups) and later by analyzing each occupation by itself for

those cancers which had at least five cancer cases. Seventeen types of cancer were screened in each occupational subgroup. They are: (1) buccal and pharynx, (2) esophagus, (3) stomach, (4) pancreas, (5) colon and rectum (combined), (6) nose, (7) larynx, (8) lungs, (9) kidney, (10) bladder, (11) testes, (12) prostate, (13) skin, (14) melanoma (skin), (15) myeloma, (16) lymphomas, (17) leukemias. For the ever exposed in the chemical group, the esophagus cancer showed an overall relative risk of 2.36 ( $P < .05$ ), an overall relative risk of 7.41 in stomach cancer ( $P < .05$ ) and two relative risks for skin cancers and malignant lymphomas both below unity and significant at the 5% probability level. There was also a relative risk of 1.65 ( $P \sim .05$ ) in buccal and pharynx carcinomas. All the remaining relative risks did not reach the level of statistical significance.

In the "five or more years of exposure" of the chemical group, there was an overall relative risk of 2.09 ( $P < .05$ ) in cancer of the larynx, an overall relative risk of 1.88 (borderline probability value) in cancer of the bladder and a relative risk of 11.12 ( $P < .01$ ) in the youngest age group (14-59) for stomach cancer, and a relative risk of 1.81 of borderline significance in the buccal cancers in the older age group (60+).

The second group (combustion series), had relative risks of 2 and above in skin melanoma but not significant at the 5% probability level. The same remark holds true for the same group if exposed to the potentially dangerous occupations for five or more years. There was a relative risk of 1.60 in cancer of stomach, of 1.98 in pancreas cancer and a relative risk of 1.77 in cancer of the nose. However, none of these values reached the level of significance. The same remark holds true for the five or more years of exposure group.

A smoking standardization was performed in both occupational subgroups, i.e. combustion and chemical. The standardization for smoking was performed within each age group and conversely the age standardization was performed within each smoking category. A simultaneous standardization over age at diagnosis and smoking habits was carried through. The overall relative risk for cancer of the larynx in the chemical group was significant at the 5% probability level.

## Specific Results in The Chemical Group (Table 1)

The results within each occupation in the chemical group (listed alphabetically), are the following:

**Barbers.** — This occupation showed an elevated age adjusted relative risk of 2.828 for cancer of the larynx which persisted also in the over five years of exposure category (relative risk 2.493). Relative risks for bladder cancer were not significant at the 5% level. The overall relative risks in larynx cancer were significant after smoking standardization in both the overall and in the "five or more years of exposure" groups (Relative risk 3.389 and 3.187, respectively).

**Operatives in the Chemical Industry.** — This occupation seemed to be highly associated with certain cancers.

Statistically significant high relative risks appeared in cancer of the larynx in the over five years of exposure group (R.R. 3.862), particularly among workers aged less than 60 (R.R. 6.750). This relative risk increased after smoking standardization in the 5 or more years of exposure (4.324, smoking adjusted vs. 3.862, age adjusted), and was still significant.

Extremely high age standardized relative risks appeared in cancer of the stomach (R.R. 4.25), particularly in the youngest age group (R.R. 11.00). Such an effect increased when the exposure

time was of at least five years, (age adjusted relative risk of 5.885, relative risks of 27.00 in the youngest age group).

**Laborers in the Chemical Industry.** — In this occupation no relative risk higher than unity was statistically significant.

**Operatives in Leather Industry.** — High relative risks appeared in carcinoma of the larynx (3.633) which increased in the over five years of exposure group (6.896). The same remark holds true for cancers of the buccal cavity and pharynx (R.R. 3.378) and bladder (R.R. 6.773 in the overall exposure which increased to 12.935 in the five or more years of exposure group). After smoking standardization in both exposure groups, the relative risks for cancer of the larynx (6.55 and 3.28), bladder (4.34 and 7.28), mouth and pharynx (3.024 and 4.848), were still significant at the 5% probability level.

**Painters.** — High relative risks appeared in both exposure groups in cancer of the esophagus (R.R. 2.994) and stomach (R.R. 2.384). The highest relative risks belonged to the age group below 60 in cancer of the stomach (12.614), and to the age group above 60 in cancer of the esophagus (3.846). There was also an increase in the relative risk in the oldest age group with cancer of the esophagus exposed five years or more (R.R. 6.875) and a relative risk of 16.615 in the age group below 60 with cancer of the stomach (five or more years of exposure). The relative risk of lung cancer (1.708) age adjusted, lost its significance after smoking adjustment in both exposure groups.

**Print Workers.** — This occupation was mainly associated with an increased incidence of cancers of the buccal cavity and pharynx (R.R. 2.586). After smoking standardization, the effect related to the occupation disappeared (overall relative risk of 2.14 (smoking adjusted) vs. 2.586 (age adjusted)). It was of borderline significance among light cigarette smokers.

*Operatives in the Rubber and Plastic Industry* did not show anything remarkable.

### Specific Results in the Combustion Group (Table 2)

The bakers showed relative risks around 2 for malignant lymphomas (not significant).

**Bus, Taxi, Truck Drivers.** — These occupations showed slightly elevated overall relative risks (buccal cavity and pharynx, stomach, pancreas and kidney). Significant relative risks appeared only in cancer of the buccal cavity and pharynx (R.R. of 2.27, in patients older than 60); a relative risk of 1.9 in the "five or more years" of exposure group appeared in the same age group. (Borderline significance) After smoking was taken into account, there was a moderate decrease in the relative risk of the oral cavity and pharynx. The highest relative risks (2.78, although not significant) came out in cancer of the pancreas in the older age group (60+).

**Delivery and Routemen.** — This occupation was not highly associated with specific cancers. There was a relative risk of 3.15 of borderline significance in skin cancer (other than melanoma). None of the other relative risks reached the level of significance.

**Kitchen Workers.** — This occupation did not seem to be hazardous.

**Locomotive Engineers and Firemen.** — Relative risks higher than unity appeared in cancers of the buccal cavity and pharynx, bladder and malignant lymphomas. However, none of these were significant at the 5% probability level.

**Mechanics and Repairmen.** — There are relative risks around 2 in cancer of the pancreas and prostate, but only the latter was significant.

*Stationary Firemen* did not show statistically significant relative risks.

**Stationary Engineers.** — None of the relative risks higher than unity was statistically significant at the 5% probability level.

### Discussion

The cancers most closely associated with specific occupations belong mainly to the digestive system, i.e. esophagus and stomach, and to a lesser extent to the respiratory system, i.e. buccal cavity, pharynx and larynx.

In general, the degree of association between cancers and occupations in the combustion group is less than that between the same cancers and the occupations of the chemical subgroup.

There are mainly two routes through which the various carcinogens reach the body tissues, i.e. the digestive route (buccal cavity and pharynx, esophagus and stomach) and the respiratory route (larynx).

Excess of cancer was also detected in the bladder. This outcome is not surprising because the bladder is a urine reservoir and its mucosa is likely to stay in contact with specific carcinogens for quite a long time.

In the combined group of chemical occupations statistically significant relative risks appeared in cancers of the esophagus and stomach. It is worth noting that the highest risk for cancer of the esophagus was in the younger age group (14-59) whereas the highest risk for cancer of the stomach was in the older age group (60+). Such an outcome may be related either to the age when the first exposure to the noxious occupations began or to the length of the exposure to the potentially dangerous occupations, or both. Possibly, the earlier the exposure age, the shorter the latency time before a neoplasia appears. These results have been confirmed also in the "more than five years" or exposure group. Significant relative risks appeared in cancer of the oral area and pharynx and bladder. (Chemical subgroup)

After standardization for age and smoking habits simultaneously, the relative risks for larynx cancer was still significant at the 5% probability level. However, the statistical significance of the relative risks in cancer of the buccal area, pharynx, lungs and bladder disappeared after the age and smoking adjustments.

None of the relative risks in the combined combustion group of occupations was significant at the 5% probability level. Relative risks higher than unity appeared in stomach, nose, kidney, bladder cancers and skin melanoma. (Combustion subgroup)

Barbers had a higher than expected incidence of carcinoma of the larynx. This is probably connected with the inhalation of fumes from cosmetics.

There is a strong suggestion that operatives of the chemical industry work in a polluted environment. High relative risks in cancers of the respiratory system and bladder may be related to the prolonged inhalation of different chemicals.

In the leather industry, smoking could not explain the high relative risks for cancer of the larynx, buccal cavity, pharynx and bladder. Moreover, the effect was strengthened over time (5 or more years of exposure). The three aforementioned cancers may be related to the tanning of leather (working hypothesis).

Among painters, the highest incidence of both cancers of the esophagus and stomach is possibly connected with the inhalation of volatile substances contained in the paints. These could either be solvents, such as benzene or trace metals (working hypothesis).

The occupations in the combustion subgroup turned out a few relative risks higher than unity but not significant at the 5% probability level. The occupations in the combustion subgroup are manifestly less dangerous, as far as cancer is concerned, than those in the chemical subgroup. It is worth noting that the

deliverymen and routemen show a relative risk of 3.15 of borderline significance in the youngest age group (14-60) in skin cancer (other than melanoma). Such an outcome may be induced by the prolonged exposure to ultraviolet radiation.

This investigation was conceived as a preliminary study over a large class of both cancers and occupations. The results obtained may warrant further studies to specify what chemical compounds may produce cancer; it would be useful to ascertain if the specific types of cancer in the same occupation may be induced by different carcinogens or whether different types of cancer may be induced by the same carcinogens but by different ages when the first exposure to the noxious occupation started. For example, certain cancers may cluster in patients whose exposure to harmful occupations started relatively early in life, whereas other malignant tumors may appear in other workers who may have been engaged in a specific occupation later in life. Higher relative risks in specific age groups may depend on when the first exposure to the dangerous occupation started. A heavier exposure to toxic substances at an earlier age when the first exposure began, may decrease the latency period before cancer develops. This may explain why certain workers get occupational cancers before age 60. Cohort studies could validate some of our results.

### Summary

It was found that the occupations most highly associated with an increased incidence of cancers belonged to the chemical subgroup. These occupations are the barbers, the operatives in the chemical industry, the operatives in the leather industry, the painters and the printers. The occupations related to the inhalation of combustion products are: The bakers, the deliverymen and routemen, the kitchen workers, the locomotive engineers, the

mechanics and repairmen, the stationary engineers and firemen.

Elevated relative risks showed up in the chemical subgroup among the barbers (cancer of the larynx), among the operatives in the chemical industry (cancers of the larynx and stomach), among the operatives in the leather industry (cancer of the oral cavity and pharynx, larynx and bladder), among the painters (esophagus and stomach) and among the print workers (cancer of the oral cavity and pharynx).

The occupations in the combustion subgroups appeared to be less associated with an increased incidence of cancers than those in the chemical subgroup. Moderately elevated relative risks appeared among the bakers in malignant lymphomas, among the bus-, taxi- and truck drivers in cancer of the pancreas, among the locomotive engineers in cancer of the buccal cavity and pharynx and lymphomas and among the mechanics and repairmen in cancers of the nose, pancreas and prostate. However, only a few relative risks were statistically significant such as skin cancer (other than melanoma, age group 14-60) and prostate cancer in mechanics and repairmen.

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