

For Cancer, Lung

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Mineral Particles, Mineral Fibers, and Lung Cancer¹

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The total fibrous and nonfibrous mineral content of the lung has been analyzed in a series of 14 men with lung cancer but no history of occupational dust exposure, and in a series of 14 control men matched for age, smoking history, and general occupational class. The lung cancer patients had an average of $525 \pm 369 \times 10^6$ exogenous mineral particles and $17.4 \pm 19.6 \times 10^6$ exogenous mineral fibers/g dry lung, while the controls had averages of 261 ± 175 mineral particles and $4.7 \pm 3.2 \times 10^6$ mineral fibers/g dry lung. These differences are statistically significant for both particles and fibers. Kaolinite, talc, mica, feldspars, and crystalline silica comprised the majority of particles of both groups. Approximately 90% of the particles were smaller than $2 \mu\text{m}$ in diameter and approximately 60% smaller than $1 \mu\text{m}$; the mean particle size in the cancer group was $1.1 \pm 0.2 \mu\text{m}$ and in the control group $1.3 \pm 0.2 \mu\text{m}$. In both groups, patients who had smoked more than 35 pack years had greater numbers of particles than patients who had smoked less than 35 pack years. It is concluded that, in this study, lungs from patients with lung cancer had statistically greater numbers of mineral particles and fibers than lungs from controls, and that smoking influences total long-term retention of particles from all sources. © 1985 Academic Press, Inc.

INTRODUCTION

Except for a few specific species such as asbestos, mineral particles are not generally considered to be carcinogens. However, a number of circumstantial observations suggest that mineral particles of a variety of types could play a role in the genesis of lung cancer in humans.

Epidemiologically, some studies have found an association between lung cancer rates and concentrations of particulate air pollutants (Doll, 1978; Hitosugi, 1968; Vena, 1982), and it has been suggested that air pollution is the factor responsible for the differences in lung cancer rates between urban and rural areas (Doll, 1978). This rate differential is probably confined to cigarette smokers (Doll, 1978; Hitosugi, 1968; Vena, 1982). It should be noted that this association is by no means universally accepted (Hammond and Garfinkel, 1980).

Experimentally, it has been demonstrated that intratracheal instillation of carcinogens such as benz(a)pyrene along with an "inert" (i.e., noncarcinogenic) mineral particle such as iron oxide greatly increases the rate of lung tumors over that found with administration of the carcinogen alone (Saffiotti *et al.*, 1972). Some other minerals such as titanium oxide, and carbon show similar effects, but not every mineral dust which has been tried is active in this system (Stenback *et*

¹ Supported by a grant from the National Cancer Institute of Canada, and grant MA7820 from the Medical Research Council of Canada.

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been analyzed in a series of dust exposure, and in a general occupational class,ogenous mineral particles. The controls had averages of fibers/g dry lung. These were Kaolinite, talc, mica, and others. Les of both groups. Ap- pproximately 1.1 $\pm$ 0.2 μ m and had smoked more than 35 cigarettes with lung cancer had lungs from controls, and in all sources. © 1985 Aca-

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relation between lung cancer and dust. Doll, 1978; Hitosugi, 1968; is the factor responsible for rural areas (Doll, 1978). smokers (Doll, 1978; His- association is by no means

tracheal instillation of car- cinogens (i.e., noncarcinogenic) rate of lung tumors over time (Saffiotti *et al.*, 1972). show similar effects, but this system (Stenback *et*

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et al., 1976). Since cigarette smoke contains both chemical carcinogens and mineral particles, a similar effect might occur in humans, and it has been shown that cigarette smoke particulates (Lubawy and Isaac, 1980), as well as a crude particulate fraction collected from the air (Warshawsky *et al.*, 1983), slow the overall metabolism of benz(a)pyrene and redirect it toward the formation of the proximate carcinogens.

Mineral particles, whether derived from cigarette smoke or from the ubiquitous number present in the air, also tend to adsorb carcinogens, and it has been demonstrated that the smallest (and hence most easily respirable) particles are the most adsorptive (Natusch *et al.*, 1974). Benzo(a)pyrene and nitrosamines have been recovered from atmospheric mineral particles (Natusch *et al.*, 1974; Kneip *et al.*, 1983). Mineral particles also appear to adsorb radioactive materials, such as the ²¹⁰Po present in cigarette smoke, and hence might deliver a carcinogenic dose of radiation to the bronchial tree (Martell, 1974; 1983).

A specific class of mineral particles, namely fibers, appears to have special carcinogenic effects which relate to size and shape, especially small size and high length to width (aspect) ratio (Stanton *et al.*, 1981). These effects are clearly seen in both humans and experimental animals in the genesis of mesothelial tumors; whether fibrous shape is important for inducing other types of tumors is not clear.

A fairly large body of experimental data has been accumulated concerning the acute phases of particle deposition in the human lung. A particularly interesting observation in this regard is the study of Schlesinger and Lippman (1978), in which a cast of the human bronchial tree was created and the deposition of particles examined. Schlesinger and Lippman showed that there was a good correlation between the number of particles deposited in different bronchi and the known relative cancer incidence in the different bronchi.

Little is known about the actual mineral content of the normal human lung, nor is there any information on regional differences in various sites, or in different diseases. Such information might shed light on the role of mineral particles in various diseases. In this study we have begun to examine the particulate content of human lungs in smokers with and without lung cancer.

MATERIALS AND METHODS

Autopsy lungs for this study were obtained from the autopsy services of the University of British Columbia Health Sciences Centre Hospital and the Vancouver General Hospital. For the test sample, 14 male cases were selected which met the following criteria: (1) a documented history of lung cancer (confirmed in all cases by pathologic examination); (2) no history of occupational or other mineral dust exposure as determined by interviews with relatives using a standardized questionnaire; (3) details of smoking history available from relatives; (4) no other pulmonary disease (except chronic obstructive lung disease) by either clinical or pathological examination. These 14 cases were matched by age (within 10 years), sex, smoking history (within 10 pack years), and general occupational category (white collar, blue collar) to 14 control cases who did not have lung cancer or a history of dust exposure. Information on the control cases was obtained from relatives using the same type of questionnaire.

All lungs were fixed in formalin. For mineralogic analysis of each case, two

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TABLE 1
AGE AND SMOKING MATCH

Group	Age (years)	Smoking (pack years)
Cancer	63 ± 11	45 ± 39
Control	63 ± 7	41 ± 21

samples of wet formalin fixed lung were taken from an upper lobe: one sample consisted of an approximately 4- to 5-g strip of pleura and underlying 0.5 cm of lung tissue. A second sample was taken at least 3 cm deep to the pleura. Data from the two samples were pooled for each case. An additional adjacent piece of tissue was taken and dried to constant weight to allow expression of results in terms of particles/g dry lung. Only grossly normal parenchyma was used.

Mineral particles and mineral fibers were isolated using a modification of the technique which we have employed previously (Churg, 1983). In brief, this consists of dissolving the lung in bleach, treating the remaining sediment with hydrogen peroxide, and collecting the mineral particles on a membrane filter. The particles are then transferred to coated electron microscope grids. Because the concentration of particles in lung is much higher than the concentration of asbestos or other mineral fibers, two different aliquots of the digested sample are prepared: a very high dilution sample for counting particles and an approximately 10- to 50-fold more concentrated sample for counting fibers.

For particle identification, approximately 200 sequentially encountered particles were counted, measured, and identified by morphology, electron diffraction, and energy dispersive X-ray spectroscopy for each sample site. Only particles with one dimension of 0.5 μ m or greater were counted in this study. For fibers, approximately 50 sequentially identified fibers (defined as particles with roughly parallel sides and an aspect ratio of 3:1 or greater) were counted for each site. Only fibers of length 0.5 μ m or greater were counted. Raw counts of particles and fibers were converted to particles and fibers/g dry lung using an algorithm relating number of grams of sample, and number of electron microscope grid squares counted. A total of approximately 11,000 mineral particles and 3000 mineral fibers was counted in this study.

Control samples were prepared for each case by running the entire preparatory procedure but omitting tissue. Control specimens contained rare short fibers of chrysotile, and scattered pieces of talc, mica, and crystalline silica. The concentration of these contaminants were so low that subtracting them from the observed values did not produce any significant change in the calculated numbers. Additional controls were prepared with the formalin which was used for fixation; essentially no particles were found in the formalin.

Statistical comparisons were made using standard *t* tests and non-parametric tests (Mann-Whitney *U* Test) on the concentration data.

RESULTS

Table 1 shows the ages and smoking histories for the cancer and control groups. For each group, 11 patients had blue collar occupations and 3 patients had white collar occupations.

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MAJOR TYPE

Mineral

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Kaolinite

Talc

Mica

Feldspars

Silica

Aluminum

Titanium

Miscellaneous^c

Total

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Iron

Apatite

* Values are given

^b Includes particle

^c NC, not calculat

TABLE 2
COMPARISON OF TOTAL MINERAL PARTICLES AND FIBERS IN LUNG CANCER CASES AND CONTROLS

Comparison	Mean concentration $\pm$ SD (counts $\times 10^6$ /g dry lung)		
	Cancer	Control	P
Total particles ^a	525 $\pm$ 367	261 $\pm$ 175	0.01
Total fibers	17 $\pm$ 20	5 $\pm$ 3	0.025

^a Exogenous particles only. See text.

Table 2 summarizes the comparison for total mineral particles and total mineral fibers between the two groups, and Tables 3 and 4 give the particle and fiber data broken down by mineral type. The data has been divided into particles and fibers which are clearly of exogenous origin, and those which are most likely of endogenous origin (see Discussion). The endogenous minerals included apatite, minerals analyzed as pure iron, and particles analyzed as iron with phosphorus, which most likely represent iron deposited on other minerals or on organic structures. The mean number of exogenous particles and the mean number of exogenous fibers was significantly higher in the cancer group ($P < 0.01$ for particles; $P < 0.025$ for fibers).

As shown in Table 3, kaolinite, talc, mica, feldspars, and silica (i.e., crystalline silica) account for about 75 to 85% of the total particles. Included in the miscellaneous group are spinels, calcium compounds (? oxalate or oxide), chlorite and vermiculite, biotite, tin, and particles which could not be identified.

Table 4 documents similar data for fibers. Asbestos fibers constituted approximately 6% of the total for the cancers and approximately 17% of the total for

TABLE 3
MAJOR TYPES OF MINERAL PARTICLE IN THE LUNGS OF CANCER AND CONTROL CASES^a

Mineral	Cancer cases		Control cases	
	Mean $\pm$ SD	% of total	Mean $\pm$ SD	% of total
Exogenous particles				
Kaolinite	135 $\pm$ 116	25.8	56 $\pm$ 61	21.4
Talc	114 $\pm$ 161	21.7	28 $\pm$ 20	10.7
Mica	103 $\pm$ 76	19.7	61 $\pm$ 87	23.4
Feldspars	58 $\pm$ 54	11.0	23 $\pm$ 13	8.8
Silica	55 $\pm$ 57	10.4	42 $\pm$ 34	16.1
Aluminum	26 $\pm$ 25	4.9	14 $\pm$ 21	5.4
Titanium	23 $\pm$ 57	4.3	8 $\pm$ 13	3.0
Miscellaneous ^b	11 (NC) ^c	2.1	29 (NC)	11.1
Total	525 $\pm$ 369		261 $\pm$ 175	
Endogenous particles				
Iron	225 $\pm$ 185		172 $\pm$ 198	
Apatite	166 $\pm$ 153		152 $\pm$ 130	

^a Values are given as particles $\times 10^6$ /g dry lung.

^b Includes particles which could not be identified.

^c NC, not calculated.

Smoking
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45 $\pm$ 39

41 $\pm$ 21

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TABLE 4
MAJOR TYPES OF MINERAL FIBERS IN THE LUNGS OF CANCER AND CONTROL CASES^a

Mineral	Cancer cases		Control cases	
	Mean $\pm$ SD	% of total	Mean $\pm$ SD	% of total
Exogenous minerals				
Chrysotile	0.4 $\pm$ 0.4	2.2	0.2 $\pm$ 0.3	4.3
Tremolite, etc. ^b	0.7 $\pm$ 0.7	4.0	0.6 $\pm$ 0.7	12.8
Amosite & crocidolite	0.02 $\pm$ 0.02	0.1	0.01 $\pm$ 0.01	0.2
Talc	1.1 $\pm$ 1.4	6.3	0.5 $\pm$ 0.5	10.6
Kaolinite	4.7 $\pm$ 8.1	27.0	0.7 $\pm$ 0.5	14.8
Mullite	0.7 $\pm$ 1.2	4.0	0.4 $\pm$ 0.6	8.5
Silica	3.9 $\pm$ 7.6	22.4	0.3 $\pm$ 0.3	6.3
Feldspars	1.5 $\pm$ 3.7	8.6	0.6 $\pm$ 0.4	12.8
Titanium	0.3 $\pm$ 0.3	1.7	0.5 $\pm$ 0.6	10.6
Aluminum	1.2 $\pm$ 3.1	6.8	0.2 $\pm$ 0.2	4.3
Miscellaneous ^c	2.9 (NC) ^d	16.7	0.7 (NC)	14.8
Total	17.4 $\pm$ 19.6	99.8	4.7 $\pm$ 3.2	100
Endogenous minerals				
Iron	4.0 $\pm$ 8.4		0.8 $\pm$ 0.6	
Apatite	0.1 $\pm$ 0.1		0.6 $\pm$ 0.6	

^a Values are given as numbers of fibers $\times 10^6$ /g dry lung.

^b Tremolite, actinolite, anthophyllite.

^c Includes particles which could not be identified.

^d NC, not calculated.

the controls. Talc, kaolinite, mullite, feldspars, silica, rutile (TiO_2) and aluminum made up the majority of the identifiable exogenous fibers.

Table 5 shows the overall size distribution for the particles in the cancer and control cases. The mean sizes and size distributions are roughly similar for both cancer and control groups. Similarly, the mean fiber sizes for the control group were: length, $1.5 \pm 1.3 \mu\text{m}$; width, $0.3 \pm 0.3 \mu\text{m}$; and aspect ratio, 6.5 ± 6.9 ; and for the cancer group: length, $1.4 \pm 1.5 \mu\text{m}$; width, $0.2 \pm 0.2 \mu\text{m}$; and aspect ratio, 8.0 ± 7.9 .

Table 6 compares overall numbers of particles in those who smoked more than 35 and those who smoked less than 35 pack years. In both cancer and control groups, the heavier smokers had more particles, but this difference was not statistically significant in either group; however, it approached significance for the groups combined (see Discussion).

TABLE 5
PARTICLE SIZE DISTRIBUTION IN CANCER AND CONTROL CASES

	Mean size $\pm$ SD (μm)	Geometric mean size (μm)	% in size range		
			<1 μm	1-2 μm	>2 μm
Cancer	1.1 $\pm$ 0.2	0.9	67.0	29.5	3.4
Control	1.3 $\pm$ 0.2	1.1	58.4	28.2	13.4

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Control cases	
mean $\pm$ SD	% of total
2 $\pm$ 0.3	4.3
6 $\pm$ 0.7	12.8
1 $\pm$ 0.01	0.2
5 $\pm$ 0.5	10.6
7 $\pm$ 0.5	14.8
4 $\pm$ 0.6	8.5
3 $\pm$ 0.3	6.3
6 $\pm$ 0.4	12.8
5 $\pm$ 0.6	10.6
2 $\pm$ 0.2	4.3
7 (NC)	14.8
4.7 $\pm$ 3.2	100
8 $\pm$ 0.6	
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% in size range		
	1-2 μ m	>2 μ m
1	29.5	3.4
	28.2	13.4

TABLE 6
TOTAL PARTICLES VS SMOKING HISTORY

Group	Less than 35 pack years	More than 35 pack years
Cancer	353 $\pm$ 412	626 $\pm$ 322
Control	216 $\pm$ 190	308 $\pm$ 159

DISCUSSION

In this paper we have presented data in two areas: baseline values for mineral particle content in the lungs of workers without occupational dust exposure; and a comparison of the mineral content in lungs of patients with and without lung cancer.

The data on mineral content show that the upper lobes of the lungs of a "normal" smoker contain an average of about 260×10^6 exogenous mineral particles and about 4.7×10^6 exogenous mineral fibers/g dry lung. The majority of the particles are composed of kaolinite, talc, mica, feldspars, and (crystalline) silica, with lesser amounts of rutile (TiO₂), and aluminum oxide. The components of the fiber burden are similar, with the addition of about 17% of the fibers in this control population composed of asbestos. Because we were interested in this study in the effects of particles which were definitely of exogenous origin, apatite and particles analysing as iron or iron with phosphorus have been excluded from our analyses. Deposition of iron or calcium phosphate (Brody and Hill, 1982) on a variety of other organic and inorganic structures, as well as generation of iron-containing particles as a result of hemorrhage into the lung, are well recognized phenomena, and there is no easy way to determine what proportion of such particles might be of exogenous origin.

We have previously published some data on the "normal" fiber burden in the general population of San Francisco (Churg, 1983); the mean number of fibers in that study was about 1×10^6 (translated into fibers/g dry lung). The reason for this difference most likely relates to the fact that, in the present report, we are counting fibers down to 0.5 μ m in length (compared to 1 μ m for the previous report), and to the fact that the previous report contained both smokers and nonsmokers and males and females (see below).

Nonetheless, two general conclusions can be drawn: (1) The majority of fiber types are more or less the same in both cities, and most likely reflect the atmospheric burden of mineral fibers in the two areas. This is certainly true of minerals such as mullite, which appear to be good markers of coal fly ash pollution. The mineral particle types found in the Vancouver population are in general comparable to published reports (Berry *et al.*, 1980) of minerals found in the atmosphere. (2) There are some differences which probably relate to the specific atmospheric pollutants encountered in the two cities. For example, the mean value for chrysotile asbestos in the San Francisco population was approximately 1.0×10^6 g/dry lung, whereas in the Vancouver population it is only 0.2×10^6 . This may reflect the fact that many large outcrops of exposed serpentine rock exist within the San Francisco Bay area. As measured by lung burden, the population of San Francisco also is exposed to attapulgite and gypsum, whereas these minerals are

virtually absent in the population of Vancouver. The reason for these differences and the source(s) of exposure in San Francisco are not clear.

Analysis of the nonfibrous particle size distribution in our cases reveals that about 90% of the particles are smaller than 2 μm in greatest diameter, and 60 to 70% are smaller than 1 μm in greatest diameter. The mean particle size of roughly 1 μm which we observed in both cancer and control patients is slightly smaller than that expected from studies of maximal acute deposition in human volunteers (generally in the range of 2 to 4 μm , reviewed in Lippmann *et al.*, 1980). This difference may reflect the size distribution of the atmospheric burden of mineral particles, or may indicate that larger particles are preferentially cleared, hence the long-term particle burden in humans is not accurately predicted by acute deposition experiments.

An interesting fact which emerges from this study, and one which requires further examination, is the suggestion of dependence of particle load on cigarette smoking. In both groups, those patients smoking more than 35 pack years had greater particle burdens than those smoking less than 35 pack years. Taking the two groups as a whole, the increase was present for most mineral types, although most marked for kaolinite and talc. This difference is not significant for the separate test and control groups, a not surprising observation given the small sample size and the evident variability of particle burden. However, if the cancer and control groups are combined, the differences for total particles approach significance, and are highly significant ($P < 0.01$) if only one patient with very few pack years but a large mineral burden is excluded as an anomalous case. Obviously this observation needs to be checked with more cases and with nonsmokers.

Two explanations can be offered for this phenomenon. First is that it reflects increased deposition from increased exposure; i.e., the number of particles presented to the lung is, in a crude way, proportional to the number of cigarettes smoked. Since the increases in concentrations of particles with increasing smoking were not limited to kaolinite, a cigarette smoke-derived particle (Brody and Craighead 1982), but were seen for most of the particle types present, and since the mean size of particles derived from cigarette smoke is only about 0.2 μm (Keith and Derrick 1960), direct deposition from cigarette smoke is unlikely to be very important.

A more likely explanation is decreased clearance of particles inhaled from all sources. Cigarette smokers in general have longer clearance times than do nonsmokers for particulates in experimental studies (Bohning *et al.*, 1982, Cohen *et al.*, 1979, and see Lippmann *et al.*, 1980 for a review), and Bohning *et al.* (1982) have, experimentally, demonstrated a strong correlation between clearance time and amount of smoking. However, there is a large individual variation in clearance times, and our data suggest that there is probably a marked variation in total long-term retention as well. Nonetheless, it appears from this study that smoking is probably a major factor in long-term particle accumulation within the lung. This could well be important in the genesis of lung cancers, since experimental studies using the inert mineral dust plus carcinogen systems (see Introduction) have shown that particles which are cleared more slowly produce more cancers than

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Our data in our cases reveals that the mean particle size of roughly 0.5 μ m in diameter, and 60 to 100 nm in diameter. This is slightly smaller than the mean particle size of roughly 0.5 μ m in diameter in human volunteers (Brody *et al.*, 1980). This suggests that the atmospheric burden of mineral particles is differentially cleared, hence the results are not as accurately predicted by acute exposure.

One explanation, and one which requires further study, is that the particle load on cigarette smokers is more than 35 pack years had by nonsmokers. Taking the most mineral types, although not significant for the separation given the small sample size, however, if the cancer and control particles approach significantly, a patient with very few pack years is an anomalous case. Obviously, the difference is with nonsmokers. First is that it reflects the number of particles present in the number of cigarettes smoked. The number of particles with increasing cigarette-derived particle (Brody particle types present, and the amount of smoke is only about 0.2 cigarettes smoke is unlikely to be the same.

If particles inhaled from all sources are cleared more rapidly than do noncancer patients (Cohen *et al.*, 1982; Cohen *et al.*, 1982; Bohning *et al.*, (1982) on between clearance time and individual variation in clearance time, a marked variation in total number of particles in the lung from this study that smoking is a major factor in lung cancer. This is since experimental studies (see Introduction) have produced more cancers than

particles cleared rapidly (Stenback and Rowland, 1978). Analogously, one could postulate that enhanced retention of carcinogenic particles because of cigarette smoking would be extremely important in the genesis of lung tumors; asbestos exposure, which combined with smoking greatly increases the incidence of carcinoma, may be a case in point.

Comparison of the cancer and control cases produces the intriguing result that the cancer cases show about twice the content of exogenous particles and about a four times the content of exogenous fibers compared to controls, and both these differences are statistically significant. A number of hypothetical explanations can be offered for this observation: (1) We have missed one or more occupational exposures in the cancer group. Although possible in the odd case (and equally possible for the control group), this theory would not explain why 10/14 cancer patients had higher total particle numbers than their matched controls. It would also be incompatible with our failure to find individual cases with huge numbers of one specific mineral type, a finding one might expect with an occult occupational exposure.

(2) The cancer patients have actually smoked more than the controls. Again, there is no reason to believe that to be true, and the fact that the heavier smokers in both groups had more particles than the lighter smokers suggests that the histories are generally accurate.

(3) However, it is entirely possible that the cancer patients smoked differently (for example, smoked down to the butt), thereby increasing their actual cigarette dose, an effect which, extrapolating from the data of Bohning *et al.*, (1982), might well increase total particle load. Alternatively, one is left with the hypothesis that the cancer patients retain more particles than noncancer patients for reasons unknown, but not necessarily related to smoking.

The possible roles of mineral particles in the genesis of lung cancer have been noted (see Introduction); our data suggest that whether the important mechanism(s) is adsorption and concentration of carcinogens (including radioactive materials) by particles, redirection of the metabolism of carcinogens, or some as yet undefined process, there is an important relationship with total number of particles present in lung tissue.

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Elizabeth L. Schmitt^{1,2}
Barbara Threatt¹

Characteristics of Breast Cancer in an Incident Cancer Population

The effectiveness of film mammography is a source of concern to radiologists because neither the ribs nor retromammary space is included on the films in good quality examinations. One hundred seven incident cancers were detected in 10,034 self-referred women followed at the University of Michigan Breast Cancer Detection Demonstration Project (UM-BCDDP) for 5 years. These cancers were analyzed for location on the film, method of detection, size, histology, and the number of films required for detection. Mammography alone detected 52 (49%) of the cancers, whereas physical examination alone detected 15 (14%). The other 40 cancers were detectable on both examinations. All of the 92 cancers detected by mammography were visible in both the mediolateral and the craniocaudal views. Only 2.2% of these cancers were within 1 cm of the posterior edge of the film in the mediolateral view; 18.7% were within 1 cm of the posterior edge in the craniocaudal view. These incident cancers were smaller, and fewer were located within the posterior 1 cm of the breast than in a similar study using the UM-BCDDP prevalent cancer population. Mammography consistently detected cancer in the breast, regardless of tumor size, histologic type, or location within the breast.

The reliability of film mammography as an effective mammographic procedure has been persistently challenged because neither the ribs nor the retromammary space is included on the films. State-of-the-art film mammography requires vigorous compression of the breast to delineate breast structures. Such compression precludes imaging of the ribs due to the curvature of the thorax.

A population screened over a period of 48 months and followed since that time, using a mammographic technique that depicted neither the ribs nor retromammary space, was used to evaluate this issue. The 10,034 self-referred women followed at the University of Michigan Breast Cancer Detection Demonstration Project (UM-BCDDP) were used for analysis. These women were screened yearly from the initiation of the project in 1974 and have been contacted annually since completion of screening in 1980. Complete information concerning medical history and follow-up is available for each woman from 1974 through the present. The prevalent cancers (79) and the interval cancers (16) were excluded from this study. This group of incident cancer screeners was an ideal group in which to evaluate the effectiveness of mammographic imaging by use of the film-screen method. The study included evaluation of the size, location, method of detection, extent of invasiveness, and number of films per examination.

Subjects and Methods

The University of Michigan BCDDP rescreened 10,034 self-referred women from June 1975 through December 1980. These women were initially screened between September 1974 and July 1976. Each patient was examined by mammography and physical examination. Independent interpretations of each testing method were made, and the examination findings were correlated. The correlated results were reported to the women and their physicians.

Mammography was performed using a dedicated Picker or a dedicated Siemens mam-

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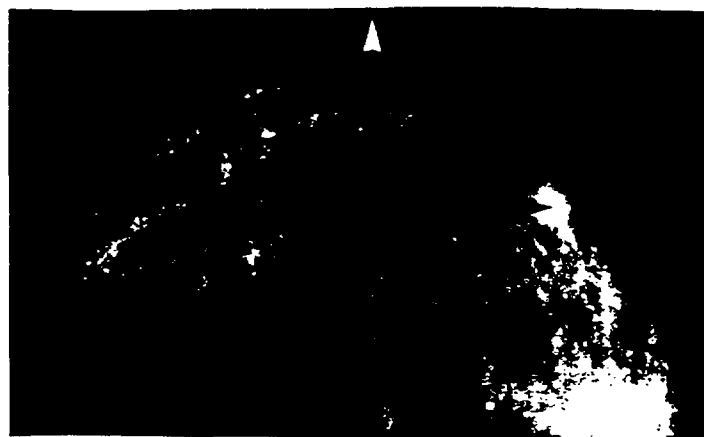
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Fig. 1.—Measuring technique on lateral (A) and craniocaudal (B) mammograms.

TABLE 2: Mammographic Abnormalities in the Mammographically Detected Cancers, University of Michigan BCDDP

	Incident Cancers 1975-1980 Abnormality No. (%)	Prevalent Cancers 1974-1978 Schmitt & Thwaitt [1], No. (%)	Wolfe [2], No. (%)
Microcalcification only	34 (37.0)	21 (28)	69 (15)
Mass with calcification	6 (6.5)	9 (12)	162 (35)
Mass/density distortion	52 (56.5)	46 (60)	231 (50)
Total	92*	76	462

* 15 cancers were undetected by mammography, including one in a patient who refused mammography.

TABLE 3: Age Distribution of Incident Cancer Screeners, University of Michigan BCDDP (1975-1980)

Age (years)	No. of Women Examined	% with Cancer	No. of Cancers (%)
35-39	1664	0.06	1 (0.9)
40-49	3876	1.0	43 (40.2)
50-59	3114	1.2	38 (35.5)
60-69	1206	1.6	20 (18.7)
70+	174	2.8	5 (4.7)
Total	10,034		107*

* There were 105 women with 107 cancers.

imaged in the juxtathoracic third of the breast in the craniocaudal view (48%) than in the mediolateral view (35%) (table 5). In the prevalent population, 59% of cancers were seen posteriorly in the craniocaudal view and 38% of the cancers posteriorly were seen in the mediolateral view. Only 2% of

TABLE 4: Method of Detection of Incident Cancers by Age, University of Michigan BCDDP (1975-1980)

Method	Age (years)		Cancers (%)
	<50, no. (%)	>50, no. (%)	
Physical only	8* (18)	7 (11)	15 (14)
Physical and mammography	19 (43)	21 (33)	40 (37)
Mammography only	17 (39)	35 (56)	52 (49)
Total	44 (41)	63 (59)	107 (100)

* Includes one woman who refused mammography.

TABLE 5: Location of Lesion on Mammogram, University of Michigan BCDDP (1975-1980)

Breast Third	No. (%) Craniocaudal	No. (%) Mediolateral
Posterior	44 (47.8)	32 (34.8)
Middle	40 (43.5)	47 (51.1)
Anterior	8 (8.7)	13 (14.1)
Total	92 (100)	92 (100)

Note.—Total detected cancers = 107; 15 (14%) were undetected by mammography, including one in a woman who refused mammography.

the incident cancers were within 1 cm of the posterior edge of the film on the mediolateral view. This contrasts with our previous study of prevalent cancers [1], in which 12% were within the posterior 1 cm of imaged breast tissue. The detected incident imaged cancers were smaller, and fewer were located in the posterior centimeter of the breast as screening continued. None of these most posteriorly located cancers was detected by physical examination alone. None of the

TABLE 6: Incident Cancer Size, University of Michigan BCDDP (1975-1980)

Size (cm)	No. (%)	Cumulative Total %
0-0.5	35 (32.7)	32.7
0.6-1.0	17 (15.9)	48.6
1.1-1.5	30 (28.0)	76.6
1.6-2.0	15 (14.0)	90.6
2.1-2.5	5 (4.7)	95.3
>2.6	5 (4.7)	100.0
Total	107 (100)	

imaged cancers required a third view of the breast for detection of the cancer.

The size of the cancer was determined by the Project pathologist from either the surgical specimen or the histologic section. Of the cancers, 48.6% were 1 cm or smaller and 76.6% were smaller than 1.5 cm (table 6). This is an increase in the number of small cancers as compared with those in our prevalent population, in which 63% were 1.5 cm or smaller. The number of detected small cancers increased with rescreening.

Of the incident cancer screenees, 85% had negative axillary nodes. Andersson et al. [5] found, in a screening project of 12,765 women aged 50-69 years, that 55% of the cancers were 1 cm or smaller and that 92.5% of these patients had negative axillary lymph nodes. This differs with the size of cancers usually found in a clinically symptomatic population, in which 19% were under 1.5 cm [6]. Physical examination alone detected 15% of the cancers under 1.0 cm and 69% were detected by mammography only (table 7). Of the cancers 0.5 cm or less, 77% were noninvasive, whereas only 10% of those over 0.5 cm were noninvasive (table 8). Mammography alone detected 76.5% of the noninvasive cancers; physical examination alone detected 5.9% of the noninvasive cancers. Mammography consistently detected noninvasive as well as invasive cancers, regardless of tumor size, histologic type, or location within the breast.

From our data, it is apparent that standard craniocaudal and mediolateral contact film mammograms properly obtained with vigorous compression will image mammographically detectable cancers in a given population. Only ten "interval" carcinomas (8.5%) occurred in years 2-5 of the UM-BCDDP. Of these 10 patients, seven did not have mammograms. Four of these seven were under age 50 and, therefore, ineligible for repeat mammograms (change of age criteria by NCI [7]) and three refused repeat mammograms. The remaining "interval" cancers (three) occurred, not because they were not imaged, but because they were obscured by the dense surrounding breast tissue (Wolfe P₂ and Dy parenchymal patterns) [4].

Vigorous compression, careful attention to positioning of

TABLE 7: Comparison of Cancer Size and Method of Detection, University of Michigan BCDDP (1975-1980)

	Tumor Size	
	≤1.0 cm, no. (%)	>1.0 cm, no. (%)
Physical only	8 (15.4)	7 (12.7)
Mammography only	36 (69.2)	16 (29.1)
Mammography and physical	8 (15.4)	32 (58.2)
Total	52 (49.0)	55 (51.0)

TABLE 8: Comparison of Tumor Size and Invasiveness, University of Michigan BCDDP (1975-1980)

Invasiveness	Tumor Size (cm)	
	0.5, no. (%)	0.5, no. (%)
Noninvasive	27 (77)	7 (10)
Invasive	8 (23)	65 (90)
% of total tumors	33	67

the breast, and proper technical factors will allow adequate imaging of cancers in any location within the breast on film-screen mammograms. This is well demonstrated in a population followed with annual screening, in which very small, early cancers were detected. Cancers detected by annual rescreening examinations are less likely to be invasive than in the prevalent cancer group. Mammography will detect small cancers consistently throughout the entire breast, including those in the juxtathoracic third of the breast. Combining physical examination and mammography enhances each method, so that the detected cancers are smaller, with a small percentage of positive lymph nodes, thereby increasing the probability of cure.

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Dr. Belk:

Attached is an article from
Environmental Research. A copy was
sent to Terry Hannan Re: E. Martinez.

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Attachment

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