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Notes

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Maternal Pattern of Reproduction and Risk of Breast Cancer in Daughters: Results From the Utah Population Database

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Background: **Several studies have found that daughters born to older mothers have an elevated risk of breast cancer, and an endocrine hypothesis, among others, has been developed to explain these findings. Three recent studies have failed to find a consistent maternal age effect, indicating a need for further exploration of this issue.** ***Purpose:*** **We used Utah breast cancer records linked to genealogical records to investigate maternal and paternal age and other maternal reproductive factors in relationship to the daughter's risk of breast cancer.** ***Methods:*** **The study group consisted of 2414 breast cancer case patients and 9138 individually matched control subjects. Breast cancer diagnoses were ascertained through the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. The case patients and control subjects were born between 1875 and the end of 1947, and the mean age at diagnosis of the case patients was 65.9 years.** ***Results:*** **No consistent effect for maternal or paternal age was found, except possibly among women who were firstborn children (odds ratio [OR] = 1.42 for a 10-year differential in maternal age; 95% confidence interval [CI] = 1.00-2.00). Further examination of the data indicated that mothers of case patients experienced long intervals between marriage and their first birth but not between subsequent births, and they went on to have fewer children. For each year of delay between the mother's marriage and first birth, the odds of breast cancer in the daughter increased 1.05-fold (95% CI = 1.01-1.10).** ***Conclusions:*** **We found no evidence of a consistent maternal age effect with regard to breast cancer risk in the daughter, but we did find evidence that the mothers of women who go on to get breast cancer have a reproductive pattern that could suggest some form of underlying infertility.** ***Implications:*** **These findings widen the epidemiologic support for the fetal antigen hypothesis, which is an immunogenetic explanation for the relationships between reproductive factors and breast cancer risk. That hypothesis provides strategies for the identification of breast cancer genes and the eventual development of a breast cancer vaccine. [J Natl Cancer Inst 86:1634-1639, 1994]**

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See "Notes" section following "References."

The association between a woman's reproductive experience and her own risk of developing breast cancer has interested researchers since the 18th century (*1*). A milestone international epidemiologic study (*2*) conducted in the 1960s provided evidence that the aspect of reproduction most responsible for this association is the age at which a woman experiences her first birth; this association is now regarded as well established (*3*). Initially, it was hypothesized to be the consequence of age-related changes in estrogen fractions during pregnancy (*4*). Later, an immunologic alternative to the strictly hormonal theory was proposed (*5*). After many years of additional research, however, the biological basis for the relationship between reproduction and breast cancer remains poorly understood.

Beginning in 1967, a series of studies have found that an older age of parents at birth, principally older maternal age, may be associated with a modest increase in risk of breast cancer in daughters (*6-11*). Proposed explanations for this association have included the age-related occurrence of germ cell mutations (*10*) and age-related differences in an intrauterine hormonal milieu (*12*). Possible immunologic explanations have not been well articulated.

The association between maternal/paternal age and breast cancer risk has not, however, been as well established as the association for age at first birth. If there is an effect for maternal/paternal age, it seems less strong than the effect for age at first birth and is therefore less readily detectable. Additionally, far fewer studies have examined maternal/paternal age, and three methodologically sound studies (*13-15*) have failed to demonstrate an effect. Further research is needed to resolve the issue.

Maternal age is only one of several features of maternal reproduction that could conceivably be examined as possible risk factors for breast cancer in daughters. In this report, we use data from Utah families to examine maternal age, paternal age, and various characteristics of the mothers' reproductive experience in relation to the occurrence of breast cancer in their daughters.

Subjects and Methods

The dataset analyzed was obtained from information in two linked files that are part of the Utah Population Database: family genealogies and cancer records. The family genealogical records were first assembled in the 1970s (*16*). They were extracted from the Family History Library (Salt Lake City, Utah), which is maintained by the Church of Jesus Christ of Latter-day Saints (LDS or Mormon). In this database, families have been linked across generations to form genealogical data. The cancer records were from the statewide Utah Cancer Registry, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.[1] The linked files allow familial and demographic information to be associated with cancer cases and have been used in numerous epidemiologic, demographic, and genetic studies (*17-19*).

The case patients selected for study were those diagnosed with a first breast cancer from 1966-1991. Of the 5624 records of cancer patients that were linked to genealogical records, 90% had information on parents and siblings, and 56% had information on case patients' spouse(s) and children. Case patients included in this study were restricted to those with full genealogical information on parents, siblings, spouses, and children; this yielded records of 2517 individuals. Nulliparous women were not included in the analysis because of the difficulty in distinguishing nulliparity from missing data regarding a woman's offspring. Further restriction eliminated 103 case patients when field checks revealed inconsistencies in the recorded data. The final file consisted of the records of 2414 case patients who were born between the beginning of 1875 and the end of 1947; the mean age at diagnosis was 65.9 years.

We attempted to obtain four control subjects per case patient. The control subjects were individually matched on birth year and birth state (Utah, Idaho, or other) and randomly selected from a pool of women in the genealogy who, like the case patients, had full genealogical records across two generations. Control subjects had no record of breast cancer and were alive at the time that the matched case patient was diagnosed. Restrictions identical to those instituted for case patients were also instituted for control subjects. After we applied these restrictions, 9138 control subjects (an average of 3.8 per case patient) were retained for analysis.

The reproductive variables used in the analysis reflect the reproductive history of both the mother and the daughter. From the mother's perspective, we calculated her age at the birth of this daughter, her total number of children (the daughter's sibship size), the birth order of the daughter within this sibship, and intervals between the mother's births. From the daughter's reproductive history, we introduced the variables of her age at first birth and her total number of children. No interviewing of case patients and control subjects was conducted for this study. Virtually 100% of the case patients and control subjects were white.

The odds ratio (OR) was used as the measure of association between reproductive variables and the risk of breast cancer. Conditional logistic regression analyses were employed to estimate ORs from the individually matched sets (*20*). Confidence intervals (CIs) (95%) around point estimates of ORs were obtained on the basis of estimated standard error of the log OR. The Statistical Analysis System (SAS) procedure PROC PHREG was employed for all calculations. Possible curvilinear relationships between reproductive variables and the log odds of developing breast cancer were evaluated by incorporating squared terms in the logistic models. Reported P values are based on two-sided testing. The relevant numbers of case patients and control subjects are given in each table, which of necessity ignores the matched relationship between individual case patients and control subjects. However, all ORs were calculated using conditional logistic regression that took appropriate account of the matched nature of the data. The numbers shown in individual tables differ somewhat from the totals of 2414 and 9138 because data on individual variables were missing or because the relevant variable applies to only a subset of the total (i.e., a minimum of two births are required in order to calculate the average interval between births). Only the adjusted estimates are reported in the tables because there was no notable difference between unadjusted estimates and those adjusted for the age at first birth and the number of children for case patients and control subjects.

Results

Table 1 gives the results for the association between the age of both mothers and fathers and the risk of breast cancer in daughters, with control for the age at first birth and the number of children of the case patient or control subject. There was little evidence of an effect for the age of either parent. When the parents' ages were included in the analysis as continuous variables, the OR for a 10-year differential in maternal age was estimated to be 1.00 (95% CI = 0.93-1.07); the corresponding estimate for paternal age was 0.99 (95% CI = 0.93-1.05). The results in Table 1 suggest a possible curvilinear relationship for maternal age, with daughters of the youngest and oldest mothers both having a lower risk than daughters of mothers who were between 25 and 39 years of age at the time of delivery. Consequently, a squared term was added to the logistic model for maternal age. The estimated curvature for the relationship between maternal age and breast cancer did not, however, achieve statistical significance (P = .09). The curvature for the relationship between paternal age and breast cancer in daughters was also within the range that would be anticipated on the basis of chance fluctuations (P = .59).

Because of a demonstrated change with age in the effects of certain risk factors (*21*), we tabulated the results regarding maternal age separately for case patients who were younger than age 50 at the time of diagnosis and for those who

Table 1. Association between parental age at birth and risk of breast cancer in daughters

Age of parent at birth, y	No. of case patients	No. of control subjects	OR* (95% CI)
Mother			
<20	128	541	1.00 (referent)
20-24	609	2386	1.05 (0.85-1.30)
25-29	682	2485	1.10 (0.89-1.37)
30-34	514	1883	1.10 (0.88-1.37)
35-39	328	1217	1.09 (0.87-1.37)
≥40	153	626	0.99 (0.76-1.28)
Total	2414	9138	
Father			
<25	345	1339	1.00 (referent)
25-29	631	2362	1.00 (0.86-1.16)
30-34	546	2161	0.96 (0.82-1.11)
35-39	431	1516	1.07 (0.91-1.25)
40-44	277	987	1.05 (0.88-1.26)
≥45	182	763	0.90 (0.74-1.10)
Total	2412	9128	

*Adjusted for age at first birth and number of children of the case patient or control subject.

were age 50 or older. As shown in Table 2, there was little evidence overall for an association. The suggestion of a curvilinear relationship between maternal age and breast cancer in the younger group and, to a lesser extent, in the older group was not found to be statistically significant when a squared term was included in the logistic models ($P = .29$ for the group that included women younger than age 50; $P = .17$ for the group that included women aged 50 years and older).

Because of high birth rates in Utah, the case patients and control subjects have a higher average birth order than would the participants in other case–control studies that have evaluated maternal age and breast cancer. To evaluate possible modification of the effect of maternal age according to birth order, we stratified the records of case patients and control subjects into those of birth order 1-3 and those of birth order 4 or greater (Table 3). In Table 3, maternal ages of 25-29 years are taken as the reference category because of the small number of women who had a birth order of 4 or greater and whose mother was also younger than age 25 at the time of the daughter's birth. These results provide little evidence for an association between maternal age at birth and risk of breast cancer within categories of birth order, as did similar analyses for paternal age (not shown). When the 546 case patients and 1935 control subjects who were firstborn children were examined as a separate group, we found some evidence for a relationship between maternal age and breast cancer (OR = 1.42 for a 10-year differential in maternal age; 95% CI = 1.00-2.00; $P = .05$).

The distributions of birth orders for the case patients and control subjects are compared in Table 4. Although the point estimates indicate that the risk of breast cancer is higher for firstborn daughters than for all but one category of women of later birth order, combining all women of later birth order for comparison with firstborn women did not provide strong statistical evidence for an association (OR = 1.08; 95% CI = 0.98-1.21; $P = 0.13$).

Results for three other aspects of the reproductive histories of the mothers of

Table 2. Association between maternal age at birth and risk of breast cancer in daughters, according to age at diagnosis

Maternal age at birth, y	Diagnosis before age 50			Diagnosis at age 50 or older		
	No. of case patients	No. of control subjects	OR* (95% CI)	No. of case patients	No. of control subjects	OR* (95% CI)
<20	16	82	1.00 (referent)	112	459	1.00 (referent)
20-24	74	285	1.33 (0.72-2.45)	535	2101	1.02 (0.81-1.28)
25-29	87	303	1.31 (0.71-2.42)	595	2182	1.07 (0.85-1.34)
30-34	58	200	1.37 (0.73-2.58)	456	1683	1.06 (0.84-1.34)
35-39	36	133	1.31 (0.67-2.55)	292	1084	1.06 (0.83-1.35)
≥40	12	66	0.87 (0.38-2.02)	141	560	0.99 (0.75-1.30)

*Adjusted for age at first birth and number of children of the case patient or control subject.

Table 3. Association between maternal age at birth and risk of breast cancer in daughters, according to daughter's birth order

Maternal age at birth, y	Birth order 1-3			Birth order ≥4		
	No. of case patients	No. of control subjects	OR* (95% CI)	No. of case patients	No. of control subjects	OR* (95% CI)
<20	127	538	0.80 (0.62-1.04)	1	3	0.93 (0.08-10.6)
20-24	574	2235	0.87 (0.74-1.02)	35	151	1.29 (0.80-2.09)
25-29	452	1536	1.00 (referent)	230	949	1.00 (referent)
30-34	149	489	0.97 (0.76-1.22)	365	1394	1.12 (0.90-1.39)
35-39	37	147	0.92 (0.60-1.39)	291	1070	1.07 (0.85-1.34)
≥40	8	26	0.71 (0.30-1.71)	145	600	0.99 (0.75-1.31)

*Adjusted for age at first birth and number of children of the case patient or control subject.

Table 4. Association between maternal reproductive patterns and risk of breast cancer in daughters

Characteristic of maternal reproduction	No. of case patients	No. of control subjects	OR* (95% CI)
Birth order of daughter			
1	546	1935	1.00 (referent)
2	425	1676	0.90 (0.78-1.03)
3	376	1360	0.98 (0.84-1.14)
4	265	1086	0.86 (0.73-1.02)
5	220	825	0.93 (0.78-1.11)
6	183	652	1.02 (0.84-1.23)
7	124	493	0.91 (0.73-1.14)
≥8	275	1111	0.88 (0.75-1.04)
Interval between mother's marriage and birth of her first child, y			
<1.0	1282	5003	1.00 (referent)
1.0-1.9	802	3022	1.04 (0.94-1.15)
2.0-2.9	142	549	1.01 (0.83-1.23)
3.0-3.9	71	182	1.51 (1.13-2.01)
4.0-4.9	23	73	1.27 (0.79-2.04)
≥5.0	41	104	1.56 (1.07-2.26)
Mean birth interval			
<2.0	313	1235	1.00 (referent)
2.0-2.9	1263	4731	1.06 (0.92-1.22)
3.0-3.9	466	1884	0.98 (0.83-1.15)
4.0-4.9	182	654	1.07 (0.87-1.33)
5.0-5.9	81	266	1.20 (0.91-1.60)
≥6.0	62	221	1.09 (0.80-1.50)
Total No. of children			
1	40	127	1.00 (referent)
2	125	389	1.00 (0.66-1.52)
3	214	687	0.98 (0.66-1.44)
4	267	920	0.91 (0.62-1.34)
5	297	1147	0.81 (0.55-1.19)
6	302	1110	0.85 (0.58-1.25)
7	247	992	0.78 (0.53-1.15)
8	225	996	0.71 (0.48-1.05)
9	246	876	0.89 (0.60-1.31)
≥10	451	1894	0.76 (0.52-1.10)

*Adjusted for age at first birth and number of children of the case patient or control subject.

case patients and control subjects are also given in Table 4: 1) the interval between the mother's marriage and the birth of her first child; 2) the average interval between the mother's remaining births; and 3) the mother's total number of children (i.e., the size of the sibship of the case patients or control subjects). For the interval between the mother's marriage and the birth of her first child, the OR for breast cancer in women whose mothers experienced an interval of at least 3 years was found to be elevated relative to the ORs of women whose mothers had their first child within 1 year of marriage. Statistically significant elevated risks were found for intervals of 3.0-3.9 years and intervals of 5.0 years or greater (OR = 1.51 and 1.56, respectively). Based on a logistic model that considered this interval as a continuously distributed variable, the OR for a differential of 1 year of this interval was estimated to be 1.06 (95% CI = 1.02-1.11; P = .01). When we compared women whose first birth occurred 3 years or later following marriage with those whose first birth occurred within 3 years of marriage, the OR was 1.45 (95% CI = 1.18-1.78).

Table 4 provides little evidence for an association between the average birth interval and the risk of breast cancer. Only women with two or more children could be included in this analysis, which considered the interval between births but not the interval following the last birth. When we treated this variable as continuous rather than as categorical, we likewise found little evidence for an association (OR = 1.02 for a 1-year differential in average time between births; 95% CI = 0.97-1.06). Table 4 does, however, provide evidence for a negative association between size of sibship and the risk of breast cancer, although none of the CIs for the individual ORs using size of one as the referent point excludes the null value. When this variable was treated as a continuous variable in the analysis, the OR for a differential of five in the size of sibship was 0.86 (95% CI = 0.78-0.95).

Because the interval between the mother's marriage and the birth of her first child and the mother's number of children are correlated, both of these variables were included together in a logistic regression analysis along with the case patient's or control subject's age at first birth and her number of children. The estimated OR was 1.05 for a differential of 1 year in the interval between mother's marriage and birth of the mother's first child (95% CI = 1.01-1.10; P = 0.03). The OR was 0.89 for a differential of five in the mother's number of children (i.e., the size of the sibship of the case patients or control subjects) (95% CI = 0.82-0.98; P = .01).

Discussion

Except for a possible effect in daughters who were firstborn, these data provide little evidence for a consistent effect of maternal age on breast cancer risk in daughters. This study is now the fourth negative study examining this possible association (*11-15*). Our findings do suggest that the mothers of women who eventually get breast cancer may experience an unusually long interval between marriage and first birth. There is no evidence that intervals between subsequent births are associated with breast cancer in daughters, but there is some evidence for a reduction in the total number of children born to women whose daughters develop the disease. Thus, the timing of the birth of the daughter herself seems not to be important; rather the results suggest that some general underlying problem in the reproductive capability of the mother may play a role in the incidence of breast cancer in daughters.

An important limitation of the current investigation is that our measures of maternal infertility are indirect ones, using reproductive events rather than accepted clinical definitions based specifically on unsuccessful attempts to become pregnant. Thus, it is possible that the observed associations are the consequence of intentional delays in reproduction, which may relate more to socioeconomic factors than to physiologic ones. It would

be important to replicate our findings using an interview study in which maternal infertility can be evaluated more directly. An additional limitation of our study is that information on nonreproductive risk factors for breast cancer was not available. Although other studies of maternal reproduction in relation to breast cancer in daughters have found little if any confounding of these associations by other risk factors, more extensive evaluation of possible bias due to confounding would of course be desirable. These potential confounders include family history of cancer, body mass, alcohol consumption, use of exogenous estrogens, and history of benign breast disease, as well as age at menarche and menopausal status. Additionally, it would be helpful if future studies included larger numbers of young women.

At least five different hypotheses or modifications of hypotheses, each invoking endocrine or immune mechanisms and each involving pregnancy characteristics or maternal reproductive characteristics, have been offered to explain various aspects of the relationship between pregnancy and breast cancer risk (*4,5,8,22,23*). None of these deals directly with the possibility that the mothers of women who eventually develop breast cancer might tend to experience some form of infertility. Among these five hypotheses, only the work of Trichopoulos (*12*) deals directly with maternal effects, and that hypothesis suggests that women born to older mothers should be at greater risk of breast cancer as the result of intrauterine exposure to high concentrations of endogenous pregnancy estrogens. Our findings do not support the epidemiological idea on which that hypothesis is based, nor does that hypothesis explain why the mothers of women who get breast cancer should experience fertility problems.

In a recent review article, Kelsey et al. (*3*) addressed the issue of a woman's history of infertility in relation to her risk of breast cancer. Infertility in the mothers of women with breast cancer was not addressed because there was no previous theoretical or empirical basis for supposing that maternal infertility might be related to breast cancer risk in the daughters. A possible link between maternal infertility and breast cancer risk in the daughter would be through some hereditary mechanism that affects breast cancer as well as fertility. We know of no evidence that such a hereditary mechanism exists, but it seems useful to consider such a possibility. Since most hypotheses about breast cancer are endocrine or estrogen related, the recent review discusses mainly hormonal infertility. Kelsey et al. (*3*) concluded that studies of infertility resulting from a hormonal abnormality that could affect breast cancer risk have yielded inconsistent results.

Of the five hypotheses mentioned earlier (*4,5,8,22,23*), one (*5*) is based on an immune rather than on an endocrine mechanism. It is called the fetal antigen hypothesis, and it provides a single explanation for the various promotional and protective relationships between reproductive factors and breast cancer risk and is not limited to the breast cancer case patient and her offspring. It also provides a mechanism to explain familial clustering of breast cancer and a way to explain infertility based on isoimmunization induced by sperm exposure or pregnancy (*24,25*), and it generally offers new immunogenetic pathways for exploration of the etiology and prevention of breast cancer. A detailed discussion of these points is presented elsewhere (*26*).

In addition to providing a framework for interpreting the current findings, the fetal antigen hypothesis also provides an alternative to the current interpretations of the association between age at first birth and breast cancer. The hypothesis incorporates the assumption that the relevant genes and their antigen byproducts are present on fetal cells and breast cancer cells. Thus, women who have their first pregnancy at an early age have a better chance of developing a protective isoimmune reaction to those antigens because they are more likely to be free of the somatic mutations that lead to breast cancer. Once these mutations occur, the immune system recognizes the gene product as self, and its ability to develop immunity to these antigens is blocked. Therefore, the chance of protective isoimmunization from a first pregnancy diminishes with age.

Genes encoding for tumor rejection antigens are being investigated in malignant melanoma for the purpose of eventual vaccine development (*27*). Identification of similar antigens that are postulated to exist for breast cancer by the fetal antigen hypothesis would also raise the potential for development of a vaccine for breast cancer. Regardless of whether one adopts primarily an immunologic or an endocrinologic view of the etiology of breast cancer, this and other studies (*6-11*) underscore the importance of examining the relationship between maternal factors, including the actual occurrence of breast cancer in mothers, and the development of breast cancer in daughters.

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Notes

[1]*Editor's note:* SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

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EXCHANGE PROGRAM

European Organization for Research and Treatment of Cancer

U.S. National Cancer Institute

The European Organization for Research and Treatment of Cancer (EORTC) and the U.S. National Cancer Institute (NCI) are offering an exchange program to enable cancer researchers to work at NCI or EORTC-related institutions for one to three years.

General Conditions

Awardees will receive an annual subsistence allowance of $30,000. Half of this amount will be provided by U.S. sources, the remainder by European sources.

European awardees will receive the U.S. contribution either from the NCI or from their extramural host institution. The European contribution of the exchangeship will be provided either by the scientist's home institution or by a European granting agency.

For American awardees, the host institution must be affiliated with the EORTC.

Documentation

The following documents are required, in English, from all applicants:

- Completed application form.
- Description of the research to be undertaken, not to exceed three typewritten pages.
- Letter of invitation from the prospective host.
- Agreement to release the applicant from the home institution for the duration of the exchangeship.
- Assurance of intention to return to the home institution at the end of the exchangeship.
- Statement concerning the provision of 50 percent of financial support by European sources. Non-EORTC member country candidates must continue at full salary at the home institution for the duration of the exchangeship.
- Three letters of recommendation mailed directly to the NCI Liaison Office by the recommending individuals.

For More Information Contact:

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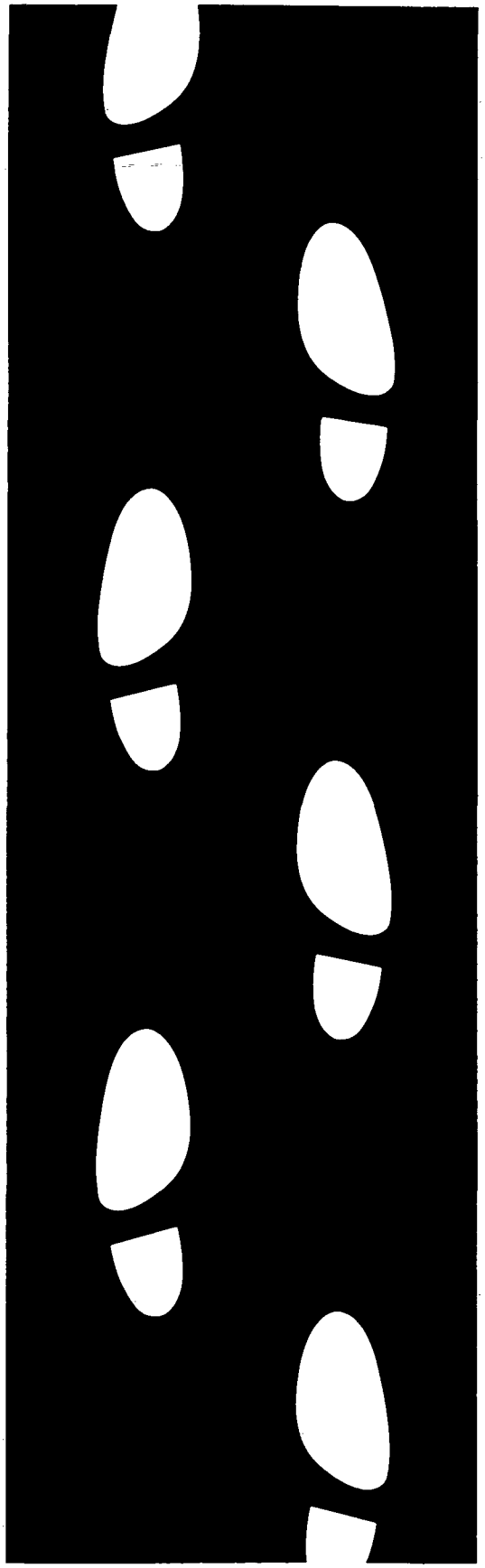

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