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REVIEW

Using Autopsy Series To Estimate the Disease "Reservoir" for Ductal Carcinoma in Situ of the Breast: How Much More Breast Cancer Can We Find?

H. Gilbert Welch, MD, MPH, and William C. Black, MD

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Purpose: To determine how many cases of breast cancer might be found if women not known to have the disease were thoroughly examined (the disease "reservoir").

Data Sources: MEDLINE search from 1966 to the present.

Study Selection: Hospital-based and forensic autopsy series examining women not known to have had breast cancer during life.

Data Extraction: Observed prevalence of occult invasive breast cancer or ductal carcinoma in situ (DCIS) in which the number of women who were given a diagnosis was the numerator and the number of women examined was the denominator. For each autopsy series, we attempted to ascertain the level of scrutiny (sampling method, number of slides examined) given to the pathologic specimens.

Data Synthesis: Among seven autopsy series of women not known to have had breast cancer during life, the median prevalence of invasive breast cancer was 1.3% (range, 0% to 1.8%) and the median prevalence of DCIS was 8.9% (range, 0% to 14.7%). Prevalences were higher among women likely to have been screened (that is, women 40 to 70 years of age). The mean number of slides examined per breast ranged from 9 to 275; series that reported higher levels of scrutiny tended to discover more cases of cancer.

Conclusions: A substantial reservoir of DCIS is undetected during life. How hard pathologists look for the disease and, perhaps, their threshold for making the diagnosis are potentially important factors in determining how many cases of DCIS are diagnosed. The latter has important implications for what it means to have the disease.

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American women have reason to believe that breast cancer is becoming more and more common. Well-intended messages designed to promote mammography may be partly responsible, but so too may a woman's own personal experience as she becomes more likely to have family or friends who are given the diagnosis. Much of this increase in incidence has been attributed to the escalating use of mammography and an enhanced ability to detect more subtle forms of cancer [1-3]. Increased detection is particularly apparent for ductal carcinoma in situ (DCIS), a relatively early form of cancer that is most often identified by mammography. Little is known about the natural history of mammographically detectable DCIS: Some cases may progress to invasive breast cancer, whereas others may not [4-6]. Such uncertainty has become more problematic because the reported incidence of DCIS has increased more than fourfold since 1980 [7]; this type of cancer now accounts for nearly half of mammographically detected cases of cancer [8, 9].

Our increased ability to detect subtle forms of breast cancer is a two-edged sword. On the one hand, it offers the hope of preventing some cases of advanced breast cancer through early detection and treatment. On the other hand, it fosters increased worry and labels more women as having disease, many of whom may never develop invasive cancer [10, 11]. It also presents clinicians with yet another uncertainty: How should these subtle forms of breast cancer be treated? In one area, however, there is little uncertainty-the ability to detect early forms of breast cancer will continue to improve.

To learn how many cases of breast cancer might be found if women were thoroughly examined, we reviewed autopsy series of women not known to have had the disease during life. The prevalence of disease observed at autopsy but undetected during life has been dubbed the disease "reservoir" by Feinstein and others [12-14]. In this article, we review efforts to define the reservoir for breast cancer and consider the effect of different prevalences on the risk for death from detected DCIS. We also discuss the role of the level of scrutiny and the pathologist's threshold for making the diagnosis.

Methods

Data Sources

We searched the MEDLINE database (1966 to the present) for English-language articles that were indexed under the Medical Subject Headings breast diseases (excluding mastitis, gynecomastia, and lactation disorders) and epidemiology or pathology. After excluding case reports, we reviewed all citations that contained the term autopsy (or autopsies) either as a subheading or in text.

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To estimate the disease reservoir, we restricted the data to autopsies performed on women not known to have had breast cancer during life. The series fell into two broad categories: hospital-based autopsies [15-18] and forensic (or "medicolegal") autopsies [19-21]. The hospital-based autopsy series often included data from women known to have had breast cancer (either cancerous breasts or breasts contralateral to those with cancer). Such series were included in our review only if the investigators presented disaggregated data that unambiguously excluded these patients. The forensic autopsy series were based on consecutive cases that were examined in the coroner's office; in these series, women known to have had breast cancer were seen infrequently. The investigators either specifically excluded such women or highlighted them (so that we could easily remove them from the numerator and denominator of the prevalence estimates). Thus, we are confident that the observed prevalences reported here apply to women who are not known to have breast cancer-that is, women who could be eligible for breast cancer screening.

Data Extraction and Analysis

To construct Table 1, we sought to determine the level of scrutiny and the findings in each autopsy series. To establish the scrutiny given to the pathologic specimens, we reviewed the method by which tissue samples were obtained for microscopic inspection and determined the average number of slides examined for each breast. We then catalogued the pathologic finding of either occult invasive breast cancer or DCIS. Because lobular carcinoma in situ has uncertain biological importance, we did not include cases of this type of cancer. Our calculation of observed prevalence used the number of women who were given a diagnosis as the numerator (we did not use the number of lesions because multifocal and bilateral lesions were regularly reported) and the number of women examined (as opposed to the number of breasts) as the denominator. To consider the effect of lower diagnostic thresholds, we also extracted the observed prevalence of potential precursor lesions (various categories of "atypia" or epithelial proliferation).

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Table 1. **Autopsy Series of Women Not Known To Have Had Breast Cancer during Life***

To improve comparability across the autopsy series, we addressed two issues. First, the age distribution varied. The Virginia series included only women older than 70 years of age [15], whereas the three forensic autopsy series [19-21] often included many young women (in one series, one quarter of the patients were younger than 25 years of age). Therefore, when possible, we also attempted to calculate prevalences for women likely to be screened (target range, 40 to 70 years of age); the precise age range was defined by the data reported. Second, information on race or ethnicity was generally poorly reported, but the series seemed to predominantly involve white women. Only women of "European descent" were included in the Australian series [19]; a similar racial or ethnic make-up is probably the case for four other series: two from Northern California [16, 18] and two from Denmark [17, 21]. Because stratification was possible, we restricted the analysis to the "Anglo" women in the New Mexico series [20], a restriction that was not possible in the Virginia series (half of whom were black) [15]. Given the available data, readers should view the observed prevalences reported here as most accurately reflecting the breast cancer reservoir in white women.

To gauge the effect of different prevalences on the risk for death from detected DCIS, we used a method described elsewhere [22]. Estimating the probability that a detected abnormality will naturally progress to death is not possible unless one can follow a cohort through time. The probability is mathematically constrained, however, by the prevalence of the detected abnormality. Calculation of the upper limit of this probability is simple when disease-specific mortality is stable (as is the case for breast cancer [23]). For example, if 12% of women 40 to 50 years of age were found to have DCIS (and given the fact that 3% of unscreened women ultimately die of breast cancer [24]), then the upper-limit probability of death from DCIS is 25% (0.03/0.12).

The actual probability is, of course, much lower. First, some cases of invasive breast cancer causing death may not arise from DCIS. Second, some 40- to 50-year-old women will have undetected invasive breast cancer, which undoubtedly is more likely to cause death. Third, some women who will die of breast cancer will have normal breasts at 50 years of age. Finally, many women with DCIS have multifocal disease, making the chance that any single detected lesion will progress to death much less likely.

Data Synthesis

Table 1 summarizes the seven autopsy series. The median observed prevalence of invasive breast cancer among women not known to have breast cancer was 1.3% (range, 0% to 1.8%). The median prevalence of DCIS was 8.9%, but the rates varied widely: One series found no cases, whereas three found DCIS in more than 10% of the women undergoing autopsy. Observed prevalences were higher among women most likely to be screened-those 40 to 70 years of age.

Review of Table 1 prompts two additional observations. First, the level of scrutiny seems related to the observed prevalences. The series that found no cases of DCIS examined nine slides per breast, whereas the two series with the highest prevalence (both of which were performed by the same investigators) were the most assiduous: The investigators examined 95 and 275 specimens per breast after being guided by radiographs of each 5-mm section. Second, a considerable reservoir of potential precursor lesions (such as atypia) was seen in women who had neither invasive breast cancer nor DCIS. Thus, if the pathologists' tendency to diagnose DCIS increased (that is, if the diagnostic threshold was lower), the prevalence of DCIS could become much higher.

Table 2 relates the effect of changing disease prevalences on the highest possible risk for dying of detected DCIS. Assuming a constant rate of death from breast cancer, an increase in the detection of DCIS decreases the likelihood that detected DCIS in any one women will be fatal. If, for example, the prevalence of DCIS in 40- to 50-year-old women is 9% (the median prevalence reported here), then the highest possible probability of death from detected

DCIS is 33%. If the prevalence of DCIS is 40% (the highest reported prevalence [21]), however, then the highest possible probability of death from detected DCIS decreases to 7.5%. It is important to emphasize that these estimates represent the worst-case scenario. The true risk could be this high only if all deaths from breast cancer were ultimately the result of DCIS present in 40- to 50-year-old women.

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Table 2. **Effect of Various Prevalences on the Upper Limit of the Risk for Death from Ductal Carcinoma in Situ in Women 40 to 50 Years of Age***

Discussion

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In 1992, an estimated 24 000 women in the United States were given a diagnosis of DCIS and 10 000 underwent mastectomy for the disease [7]. The autopsy series reviewed here, however, suggest that the disease reservoir for DCIS is substantial and that many more cases could be detected. In 1992, approximately 40 million U.S. women were at an age at which screening might be recommended (40 to 70 years of age). If the underlying prevalence of DCIS is truly 5% (a reasonable lower-bound estimate, given the findings of six of the seven series reported here), then 2 million U.S. women could be found to have the disease if they are sufficiently scrutinized (for example, by use of digital mammography and magnetic resonance imaging).

Understanding the size of the DCIS reservoir is important because the reservoir provides insight into what it means to have the disease and how aggressively the disease should be treated. Although some argue that DCIS generally progresses to overt breast cancer and must be found and treated [25, 26], others suggest that its course varies and that current therapy may be too aggressive [7, 27]. If the reservoir is small, it is possible that DCIS is an aggressive lesion and that the proponents of aggressive therapy are correct. If the reservoir is large, then the mathematical constraints result in a small probability that an adverse outcome would occur if DCIS was detected; this should encourage us to rethink the current diagnostic and therapeutic approach to the lesion.

Although the data we reviewed suggest that a large reservoir of DCIS is likely, the range of observed prevalences is disconcerting. Part of the variability is undoubtedly explained by the imprecision of estimates obtained from relatively small samples. In addition, the underlying populations from which the samples were drawn may differ, despite our efforts to increase comparability across studies. Some of the explanation for the variability, however, concerns the pathologists' level of scrutiny: Those who looked harder found more. The highest prevalences observed were associated with examining numerous specimens by radiographic guidance [17, 21]. Not surprisingly, when one series that did not use thin-section radiography was repeated after the technique was used, more cases of cancer were found [28]. Because pathologic specimens can never be completely sampled, actual prevalences of DCIS may be even higher than those reported here.

Finally, the possibility that pathologists have different thresholds for diagnosing DCIS must be considered. It is important to recognize that the lesions in question are small (generally < 5 mm in diameter) and that, at the margin, the distinction between cancer and no cancer can be subtle. The one series [18] that described the distinction between DCIS and severe ductal atypia acknowledged that the distinction could not be made on the basis of subgross appearance and that the histologic appearance of severe ductal atypia "is similar to DCIS, although the pathologic alterations of the former are somewhat less marked" [18]. Given these subtleties, it is reasonable to wonder how often pathologists agree on the diagnosis of DCIS.

Schnitt and colleagues [29] performed such a study with six pathologists who had considerable experience in diagnostic breast pathology. To maximize agreement, each pathologist was given a written set of guidelines and diagrams on the criteria for three categories of proliferative ductal breast lesions. They also received a set of 15 teaching slides (5 examples of each lesion) and a set of 24 study slides (selected only if they were of "high technical quality and free of artifacts"), on which masking tape covered all but the area to be evaluated. This ensured that each observer was looking at the same area of the slide.

Despite this effort, there was some disagreement about whether DCIS was present in one third of cases (8 of 24). The Figure 1 shows the 10 cases in which at least one pathologist diagnosed DCIS. The pathologists completely agreed on only 2 cases. The propensity to make the diagnosis seemed to vary across pathologists (range, 3 in 24 to 8 in 24). Disagreement was even more pronounced in a similar study of five pathologists who had expertise in breast disease and were asked to apply the diagnostic criteria used in their daily practice [30].

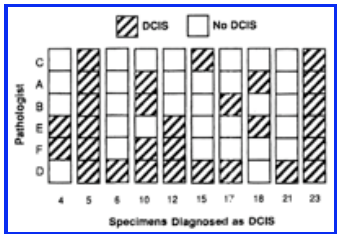

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Figure 1. **Results of Schnitt and colleagues' study ([29]) on interobserver agreement in the 10 cases in which at least one of six pathologists diagnosed ductal carcinoma in situ (DCIS).** Striped squares represent a DCIS diagnosis. The pathologists are ordered according to increasing propensity to diagnose DCIS. Agreement was much more common in the remaining cases (12 of 14), in which no pathologist diagnosed DCIS.

Given the potential size of the DCIS reservoir, such lack of agreement on the diagnostic threshold is of particularly concern because it may be relevant to so many persons. Pathologic interpretation, however, is not the only source of variability along the diagnostic pathway to DCIS. The specimens presented to pathologists are the result of a decision to perform biopsy; this decision is primarily influenced by the recommendations of mammographers, a group in whom disagreement about who should have biopsy has also been documented [8, 31].

To definitively characterize the DCIS reservoir, a large prospective study of the age-specific prevalence of occult breast cancer is sorely needed. In the interim, however, it is important to use the available data. Although our review is clearly limited by the inconsistencies of existing data and may apply only to white women, it nonetheless suggests that a substantial reservoir of DCIS probably exists. A large disease reservoir would imply a highly favorable prognosis and might be an argument for increasing the diagnostic thresholds for DCIS, despite the strong forces favoring the opposite because of such factors as fear of a failure to diagnose cancer and malpractice concerns. Finding the balance between detecting subtle precancerous lesions that would ultimately matter to patients while avoiding overdiagnosis will require more precise data on the size of the underlying disease reservoir and its relation to mammographic and pathologic interpretation.

Dr. Black: Center for the Evaluative Clinical Sciences, Dartmouth Medical School, 7250 Strasenburgh, Hanover, NH 03755-3863.

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From the Department of Veterans Affairs Medical Center, White River Junction, Vermont; Dartmouth Medical School, Hanover, New Hampshire; and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.
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Requests for Reprints: H. Gilbert Welch, MD, MPH, VA Outcomes Group (111B), Department of Veterans Affairs Medical Center, White River Junction, VT 05009.
Current Author Addresses: Dr. Welch: VA Outcomes Group (111B), Department of Veterans Affairs Medical Center, White River Junction, VT 05009.

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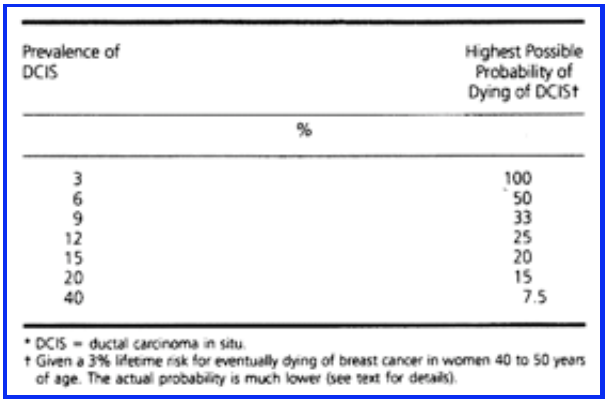
Table 1. **Autopsy Series of Women Not Known To Have Had Breast Cancer during Life***

Location, Year (Reference)	Patients (Type of Autopsy)	Level of Scrutiny		Observed Prevalence			
		Specimen Sampling Method	Mean Slides per Breast	Of IBC (95% CI)	Of DCIS (95% CI)	In Women of Screening Age (40–70 years)	Of Potential Precursor Lesions in Women without Cancer
	n		*n*	%			
Virginia, 1973 (15)	70 (Hospital)	ND	40	1.4 (0–7.7)	4.3 (0.9–12.0)	All women >age 70 y	10% had "atypical hyperplasia"; 27% had "severe hyperplasia"
California, 1975 (16)	67 (Hospital)†	Directed by subgross inspection of 2-mm sections‡	ND	0 (0–5.4)	4.5 (0.9–12.5)	10% had DCIS (age 50–70 y)	ND
Denmark, 1984 (17)	77 (Hospital)	Directed by radiographic appearance of 3-mm sections	95	1.3 (0–7.0)	14.3 (7.4–24.1)	ND	3% had "atypical ductal hyperplasia"
California, 1985 (18)	101 (Hospital)	Directed by subgross inspection of 2-mm sections‡	ND	0 (0–3.6)	8.9 (4.2–16.2)	13% had DCIS (age 40–70 y)	Only found in patients with DCIS
Australia, 1985 (19)	207 (Forensic)	At least 2 samples from each quadrant and 2 samples from central zone	11	1.4 (0.3–4.2)	12.1 (8.0–17.3)	ND	13% had "atypical hyperplasia"; 27% had "moderate–severe hyperplasia"
New Mexico, 1987 (20)	221 (Forensic)	1 sample from nipple, 1 "representative" sample from each quadrant, 1 "random" sample from each quadrant	9	1.8 (0.5–4.6)	0 (0–1.7)	7% had IBC (age 45–54 y)	10% had "marked" intraductal hyperplasia; 25% had "moderate" intraductal hyperplasia (age 45–54 y)
Denmark, 1987 (21)	109 (Forensic)	Directed by radiographic appearance of 5-mm sections	275	0.9 (0–5.0)	14.7 (8.6–22.7)	39% had DCIS (age 40–49 y)	12% had "atypical ductal hyperplasia" (age 40–49 y)

* DCIS = ductal carcinoma in situ; IBC = invasive breast cancer; ND = not described.
† Reported as number of breasts, not number of women. Prevalences are therefore the percentage of breasts, not the percentage of women.
‡ On subgross inspection, specimens were placed in plastic bags and viewed by using a dissecting microscope.

Table 2. **Effect of Various Prevalences on the Upper Limit of the Risk for Death from Ductal Carcinoma in Situ in Women 40 to 50 Years of Age***



Prevalence of DCIS	Highest Possible Probability of Dying of DCIS†
%	
3	100
6	50
9	33
12	25
15	20
20	15
40	7.5

* DCIS = ductal carcinoma in situ.
† Given a 3% lifetime risk for eventually dying of breast cancer in women 40 to 50 years of age. The actual probability is much lower (see text for details).

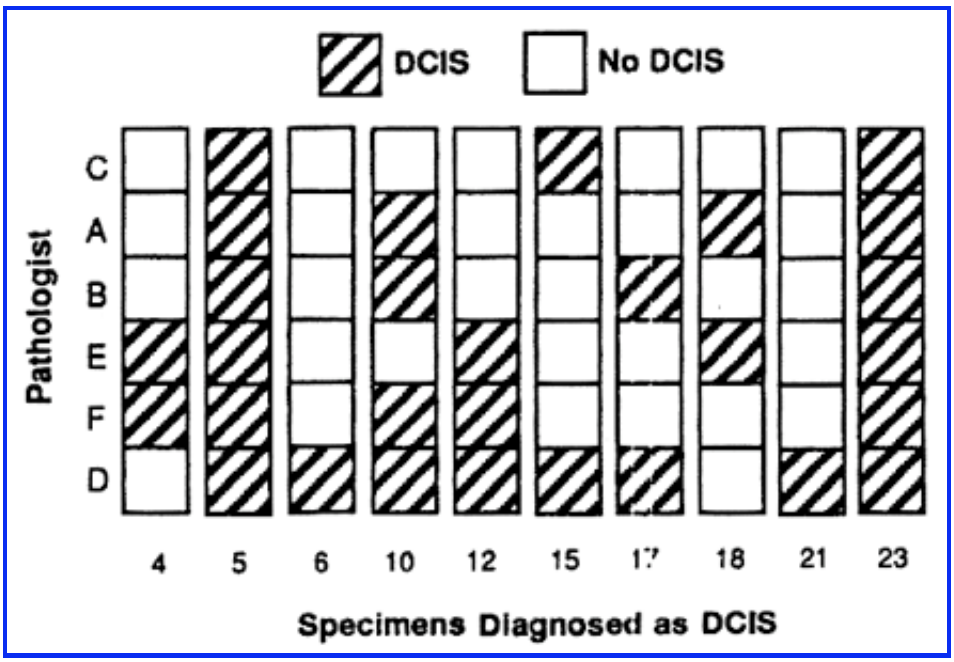


Figure 1. **Results of Schnitt and colleagues' study (** [29] **) on interobserver agreement in the 10 cases in which at least one of six pathologists diagnosed ductal carcinoma in situ (DCIS).** Striped squares represent a DCIS diagnosis. The pathologists are ordered according to increasing propensity to diagnose DCIS. Agreement was much more common in the remaining cases (12 of 14), in which no pathologist diagnosed DCIS.