Journal of Cellular Biochemistry, Supplement 16G:175-182 (1992)

Indicators of Increased Breast Cancer Risk In Humans

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Abstract Specific atypical histological patterns of epithelial hyperplasia (AH) indicate a medically relevant risk of breast cancer development in 5-10% of women with otherwise benign biopsies. This risk is about four times that of similar women, *i.e.*, of the same age and at risk for the same length of time. These relative risks are not stable with time and fall 10-15 years after detection. Absolute risk for invasive breast cancer after AH is about 10% in 10-15 years after biopsy and is most certain for perimenopausal women. Proliferative disease without atypia predicts only a slight elevation of risk with a relative risk (RR) of 1.5 to 2 times that of the general population.

There is such a strong interaction between family history and AH that it is relevant to consider women with atypical hyperplasia who have a positive family history (FH) of breast cancer separately from those who do not. The absolute risk of breast cancer development in women with AH without a FH was 8% in 10 years (RR about 4), whereas those with a positive family history experienced a risk of about 20% at 15 years (RR of about 10). This interaction of AH and FH has also been observed in other recent studies.

Low replacement doses of conjugated estrogen after menopause do not further elevate risk beyond that identified by histology. In our cohort of over 10,000 women who underwent benign breast biopsy in Nashville, TN, we found no association between proliferative breast disease without atypia and a first-degree FH of breast cancer; the prevalence of these lesions was 27% and 29% in women with and without such a history, respectively. Women with this family history did, however, have a higher prevalence of AH than did women without this history (4.8% versus 3.9%, respectively; p=0.02). It would appear that these histologic lesions are not due to an estrogen effect, but are an unrelated phenomenon, and that FH of breast cancer is not related to the proliferative lesions associated with only slightly increased risk of breast cancer.

Key words: atypical hyperplasia, breast cancer, cancer risk, family history, hyperplasia, premalignancy, proliferative disease

"Preneoplasia" or "premalignancy" usually supposes that there are identifiable lesions which may progress in some fashion through stages to eventuate in life-threatening neoplastic disease. In actuality, most lesions which we so recognize in humans have obtained their premalignant implication as indicators of increased risk. This comes from follow-up studies in which predictiveness is tested. It is appropriate to recognize at least two categories of premalignancy. One would be indicators or markers of increased risk, and the other would be lesions which are themselves committed in a large percent of cases to progress to invasion and metastasis. This presentation will review premalignancy, emphasizing information from human breast cancer relevant to assessment of breast cancer risk and its relevance to prevention strategies.

To the theoretical construct of precursors should be added the important phrase and concept "non-obligate precursors" [1]. Certainly, this recognition of less than fully committed lesions is more relevant to some lesions than others. It is a concept still accepting linear development from a precursor to a "real cancer" but recognizing that many do not complete the path (Fig. 1). Note that the path is undoubtedly complex as it ends in solid tumors with the attainment by a clone(s) of cells of many attributes which, most simply, are:

1) Growth beyond normal control,
2) Invasion into stroma,
3) Metastasis and survival of tumor cells to grow at distant sites and threaten life. Such a group of cells with this capacity and attainment may be defined as "fully malignant".

One useful approach to the general concept of premalignancy is to accept the precarious nature of prediction and use a complex paradigm that includes several models of cancer development. Rather than considering the points or plateaus on Fig. 1 as elements programmed to progress, we should think of them as

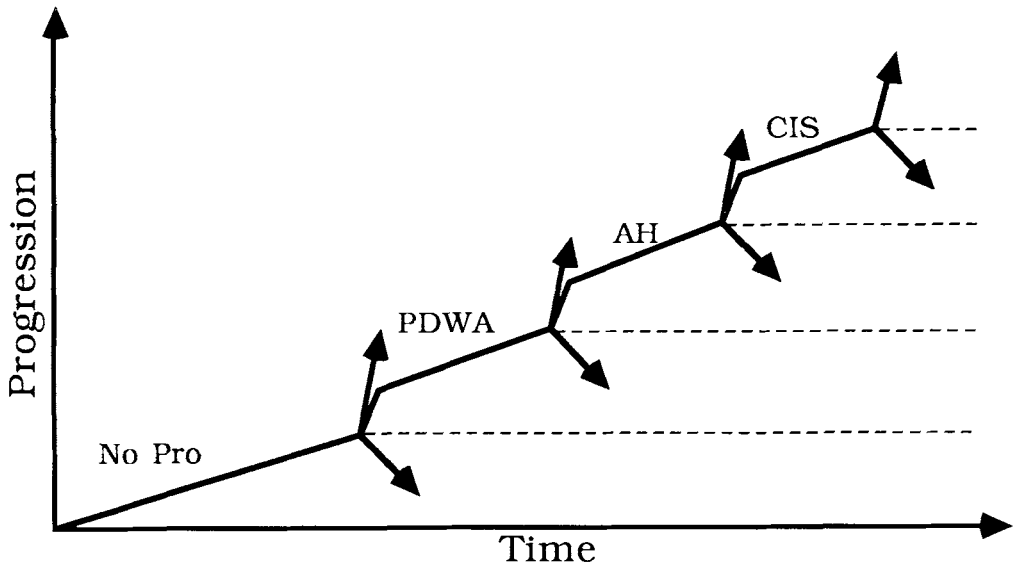

Fig 1. Model for premalignant conditions, highlighting magnitude of risk for progression to clinical malignancy. Terms from human breast neoplasia are used:

No Pro = no proliferative disease
PDWA = proliferative disease without atypia.
AH = typical hyperplasia
CIS = carcinoma *in situ*

As is the proposal of tumor progression each stage is more likely to proceed to the next (dotted lines), but could also remain stable (horizontal lines, probably fairly frequent), or directly proceed to develop a clone of cells with malignant behavior (vertical lines, becoming more likely further to right.

intermediate endpoints or markers sufficiently related to the development of cancer so that they may be useful in the study of cancer development [2]. The certainty of association with carcinoma probably increases with the magnitude of risk identified and thus the levels of "progression" in Fig. 1 are largely determined by magnitude of risk which they identify. Also, the certainty is much greater if the risk predicts local occurrence of the later developing carcinoma. The last scenario would be a true precursor lesion.

In the realm of premalignancy, we are largely left with the realization that any approach is less than all-embracing. In other words, it is impossible to predict with complete certainty the development of the fully malignant phenotype from any lesion which has not already attained these features [3]. In fact, there are well-documented situations in which after malignancy has been fully attained, including distant metastases, regression has occurred [4]. This possibility for carcinoma *in situ* is referenced in Fig. 1, similar to the model of cancer development proposed by Leslie Foulds [4], and it is evident that both stability and regression may occur at any stage but become less likely with progression.

James Ewing recognized different types of lesions with premalignant significance and entitled his 1914 paper: "Precancerous Diseases and Precancerous Lesions, Especially in the Breast" [5]. Ewing wrote: "... certain pathological conditions are followed in a variable but high proportion of cases by carcinoma...but it should be emphasized that these diseases possess in themselves not a single essential element of the cancerous process. They are merely observed to precede and favor the development of cancer." One intent of his review was to separate precancerous diseases (also termed precancerous conditions) from the cellular populations which pass "by the many transitional stages... into cancer." Thus, chronic mastitis is a condition felt precancerous and separable from the morphologically defined "... suspicious changes suggesting carcinoma." The former may be regarded as fertile soil for cancer development and the latter as suggested true precursor lesions because of anatomic transition.

Ewing's own observations and citations from the work of others included predominantly concurrent observations only, i.e., lesions associated with established cancers present at the time of cancer

TABLE 1

SUMMARY OF RESULTS FROM COHORT STUDIES OF HISTOLOGICALLY DEFINED BENIGN BREAST DISEASE

Histological Diagnosis	No. Patients	RR
Dupont and Page		
Entire Group	3,303	1.5
Atypical hyperplasia (AH)	232	4.4
Proliferative disease without atypia (PDWA)	1,693	1.6
Lacking proliferative changes	1,378	0.89
Kodlin, et. al.		
Entire group	2,931	2.7
Black-Chabon atypia-4	49	6.0
Black-Chabon atypia-3	262	2.4
Black-Chabon atypia-1-2	2,092	2.3
Papiloma, intraductal	80	5.0
Carter, et. al.		
Entire group	16,692	
Non-proliferative	3,914	1.5
Proliferative	8,772	1.9
Atypical hyperplasia	1,305	3.0
Tavassoli and Norris		
ADH	82	4-5(range)
Euscbi, et. al.		
Entire group	4,397	
"Clinging carcinoma"(like ADH)	21	4.3
Connolly, et. al.		
PDWA	2.0	
AH	5.3	

diagnosis. While these studies have given us a great deal of fundamental information [6], and established most of the diagnostic terms and concepts in general use [7], they cannot indicate the predictive power in the future for cancer deriving from the presence of any lesions or conditions when discovered without cancer [8].

Cohort studies with a follow-up design provide information on the predictive power of risk indicators. Their weakness is that identification requires removal of the marker lesions. These cohort studies may be prospective in design with regard to histologic data when that information is evaluated in its original form in histologic material from biopsies. Despite some differences in histologic criteria, agreement is uniform in general principles, and has consistently supported the assignment of increasing risk of breast cancer to more extensive and complex examples of epithelial hyperplasia (Table 1). Our evaluation of the histologic evidence is rigorous, and demands combined criteria of histologic pattern and cytologic features. Our estimates [9,10] of both the incidence and relative risk of atypical hyperplasia are in rough agreement with that reported by Kodlin et. al. [11] for lesions with a Black-Chabon atypia [12] score of 4 (the designation closest to atypical hyperplasia of our studies). The incidence of 2% for grade 4 lesions found by Kodlin et. al. [11] compares relatively closely with our incidence of atypical hyperplasia in 3.6% of 10,366 benign breast biopsies. This latter study re-evaluated biopsies performed in Nashville's largest hospitals between 1950 and 1968, obtained a 85% successful follow-up with a median of 17 years and found 135 women who developed invasive carcinoma of the breast [9]. Carter et. al. [13] using truly retrospective histologic data (from original surgical pathology reports) from the Breast Cancer Detection Demonstration Project found a greater clustering or less separation of risk for histologic categories (see Table 1) as would be expected from the less rigorous and less consistent histologic analysis of many different surgical

TABLE 2

ANATOMIC LESION TYPES IN THE HUMAN BREAST
WITH PREMALIGNANT IMPLICATION

Marker or indicator of generalized increased risk:

ALH, ADH, LCIS.

Varied risk magnitude (LCIS>AH).
Applies to any site in remaining breasts.

Determinant lesion with regional risk:

Non-comedo DCIS

Non-obligate, but frequent precursor of local invasive carcinoma.

Largely committed to invasion and metastasis:

Comedo DCIS

High likelihood to be associated with local invasion and metastasis concurrently in region or soon after discovery.

pathologists without agreement on criteria. However, the trend is evident, and family history of breast cancer also significantly increased breast cancer risk over that identified by histologic category alone in both the Carter et. al. [13] and Dupont and Page [9] follow-up studies. Age at first birth is also interactive with anatomic risk factors [14].

The aim of this has been to link anatomic terms to levels of malignancy risk, providing a framework to which other markers may be added to increase precision or replace the anatomic ones, but the linkage to specific events in human populations will remain a necessary link for non-anatomic makers until primary prevention is possible. Even this risk assessment approach must be tempered with judgment, all of the relative risk statements here stated should be greatly increased if the comparison population were at low risk. Within our own studies the comparison groups taken to be representative of the general population have used data from the Connecticut Tumor Registry [14], the Third National Cancer Survey [10,15] as well as women from within our own study population [9]. Each of these approaches has produced similar magnitudes of relative cancer risk for each lesion studied.

Reviewing the evidence from current knowledge of the human breast [16] we may offer a different construct which includes regionality of risk (local v. diffuse) as well as magnitude of cancer risk (Table 2). Here, atypical hyperplasia (AH) and the higher risk indicator lobular carcinoma *in situ* (LCIS) are regarded as only markers of general breast cancer risk because the later developing breast cancers may be in any site in either breast.

Proliferative Breast Disease

The diagnostic phrase proliferative breast disease indicates that there are proliferative alterations noted by histology, and that they indicate a disease by their demonstrated link to an increased risk of subsequent carcinoma development. The risk categories may be stratified into slight, moderate and marked, with "slight" indicating a risk approaching double that of the general population and "marked" indicating about a ten fold increased risk. The attempt to link rigorously defined categories with risk statements leads to some apparent terminologic inconsistencies in that the variety of alternatives is not reducible to an even spectrum, but it is our intent to recognize reproducible entities and seek their risk assessment individually (Table 1 and Table 2).

Slightly Increased Risk

The magnitude of risk elevation in this slightly elevated group is reliably increased more than 50% over that of women of similar age from the general population. However, risk of developing invasive carcinoma in the next ten to fifteen years does not reliably attain the magnitude of 100% greater or double that of the reference population. This range of risk may be recorded as 1.5-2.0 times that of the general population, and indicates that the risk assessment or assignment is not specific, but rather probabalistic. The magnitude of the relative risk depends largely on the populations used for comparison. Thus, we found a risk elevation of 1.6 times when the general population was used as a comparison group, and 1.9 when women from our study with only mild or no hyperplasia were the comparison population [9]. It is likely that use of the term "premalignancy' for this group is inappropriate.

The major histologic patterns and categories contained in this slight elevation of risk category are the more developed, usual or common types of epithelial hyperplasia. The terms "papillomatosis" and "epitheliosis" have been used for these changes [17]. These later terms will still find utility, but have caused confusion and are inconsistently applied, at least among countries. The intent of the term "usual" is to relay the idea that these are the commonly found patterns of cytology and cell relationships seen when cell numbers are increased within the basement membrane-bound spaces within the human breast. These alterations are most common in the immediate pre-menopausal ages. Hyperplastic lesions indicating a slight cancer risk should be further understood to mean proliferative disease without atypia, PDWA, to separate them from the next group qualified by a greater magnitude of risk. Of course, they also lack the qualitative and quantitative histologic features of atypical hyperplasia [18].

Moderately Increased Risk

This term was chosen by a 1985 consensus conference [19] in order to place these lesions in perspective between those noted above and microscopic examples of *in situ* carcinoma. The relative risk for subsequent invasive carcinoma of the atypical hyperplasias within this group is four to five times that of the general population. This is approximately half the risk experienced by women with microscopic *in situ* carcinoma. Although the current system of classification was largely developed using the Wellings and Jensen system [6] as a template, their category of "4" was not useful in determining as high a risk of breast cancer as the combined cytologic and histologic pattern criteria used in the Nashville studies [20].

The atypical hyperplastic lesions which comprise this moderate risk group are recognized histologically by their close resemblance to lesions long recognized as carcinoma *in situ*. They are named by analogy to lobular carcinoma *in situ* and ductal carcinoma *in situ* respectively. The atypical hyperplasias, as defined in this manner, may be viewed as having some of the same features as the carcinoma *in situ* lesions, but in less than fully developed form [10,18]. Criteria of histologic pattern, cytology and extent of lesions are all used [10,18]. The categories produced by this separation were then tested in a prospective, epidemiologic setting and found to indicate different levels of risk (Table 1). Lobular carcinoma *in situ* is recognized where there is a well developed example of filling, distention, and distortion of over half the acini of a lobular unit by a uniform population of characteristic cells. This follows the approach of the original description [21]. Atypical lobular hyperplasia is recognized when more than half the acini are not completely distended, or filled by the uniform population of characteristic cells or both.

Each type of atypical hyperplasia was found in the follow-up to indicate an increased risk of breast cancer in the range of four to five times that of the general population. The absolute risk of breast cancer development in women with atypical hyperplasia without a family history was 8% in 10 years. The risk for subsequent breast carcinoma development is equally distributed between either breast for both lesions of atypical lobular and atypical ductal hyperplasia. Both the level of risk for AH and the even bilateral distribution of later cancers is supported in a recent study of follow-up design [22]. Another aspect of elevated risk which is seen in the Nashville studies as a by-product of the extended length of follow-up is the fact that some elevated risk indicators are not stable with time. At least when measured as relative risk using instantaneous hazard functions, the relative risk was much higher during the first ten years after biopsy than it was in the years succeeding that initial period. This fall in relative risk with advancing time since initial biopsy, and obviously individual patient age, was seen for both the combined slight increased lesions in the proliferative disease without atypia category as well as in the higher risk category indicated by atypical hyperplasia [23]. This finding of variation of relative risk with time would indicate that this should be considered as a co-variate in some future studies.

Family History

There was such a strong interaction with family history in our major study [9] that it is relevant to consider women with atypical hyperplasia who have a positive family history of breast cancer separately from those who do not.

Women with a positive family history experienced a risk of invasive breast cancer of about 25% at 15 years. This strong interaction with family history has been supported in two recent studies [13,22]. Most recently, the Nurses Health Study from Harvard evaluated prior benign breast biopsies by the criteria of Page et. al. [10,18] and confirmed the same risk associations of AH for later invasive breast cancer [22]. Specifically, the average time from benign breast biopsy to development of cancer was 11 years. The relative risk of subsequent breast cancer for women with PDWA was 2.0 (95% CI 1.0-3.8; $p = 0.05$) whereas women with atypical hyperplasia) had a relative risk of 5.3 (95% CI 2.4-11.8; $p = <0.001$). The reference group used as the denominator was the group with no proliferative disease indicators at biopsy.

In our cohort of more than 10,000 women who underwent benign breast biopsy we found no association between proliferative breast disease (PBD) without atypia and a first degree family history of breast cancer; the prevalence of these lesions was 27% and 29% in women with and without such a history, respectively. Women with this family history did,

however, have a higher prevalence of atypical hyperplasia [24] than did women without this history (4.8% and 3.9% respectively, P = 0.02).

Lesions of Greatly Increased Risk

Histological lesions qualifying for this category are microscopic examples of ductal carcinoma *in situ* and lobular carcinoma *in situ*. Note that larger lesions comprising a dominant mass produced by ductal carcinoma *in situ*, particularly comedo ductal carcinoma *in situ*, are considered true cancers and are not included in this category of high risk lesions.

A recently reported study from Northern Italy notes a four times greater risk for later invasive carcinoma in women with carcinoma *in situ* at biopsy [25] with a mean length of follow-up of 16 years. Sixty of 4,397 originally diagnosed as benign biopsies were diagnosed as either: ductal carcinoma *in situ* (DCIS), LCIS or "clinging carcinoma." This last category appears to overlap significantly with atypical ductal hyperplasia as used in our studies, although with an incidence of somewhat less than one-half that of our studies (0.48%vs 2.1%) it is evident they are not completely comparable.

Lobular carcinoma *in situ* (LCIS) is the classic example of a greatly increased risk lesion identifying a high risk of subsequent carcinoma development in either breast. The predictive value of lobular carcinoma *in situ* is recorded in several studies, and recognizes increased risk in the range of 7 to 9 times that of the general population. No interaction to increase the magnitude of risk further has been recognized, even for the concurrence of a positive family history of breast cancer and LCIS [26].

Our understanding of the natural history of microscopic examples of ductal carcinoma *in situ* comes largely from two studies published in 1978 and 1982 [27,28]. Each of these studies reviewed a large number of breast biopsy specimens previously recognized as benign and identified a total of almost 60 cases of microscopic and non-comedo ductal carcinoma *in situ*. Follow-up of these women demonstrated an absolute risk of breast cancer development between 25 and 30% in 15 years. The relative risk of this experience was about 10 times that of the general population. Importantly, both studies were in total agreement that subsequent invasive carcinoma occurred in the same area of the breast as the originally identified carcinoma *in situ* lesions. This strongly indicates that such lesions are predominantly monofocal as tested by the biology of long term follow-up.

Comedo type of CIS has long been recognized as a special lesion in the human breast. Since the latter part of the 19th century it has been regarded as "cancer". When treated by local excision [29], at least 50% recur within three years, usually with invasive disease. This is only true for the large, palpable examples which were relatively common before mammography and now make up only a minority of lesions diagnosed as DCIS [30,31]. There is a close relationship between comedo DCIS and the c-erbB-2 oncogene expression [32], stronger than for invasive carcinoma. The functional correlates of this observation are not yet clear, but Cardiff has demonstrated that oncogene overexpression is related to tumor morphology in a murine, transgenic model [33], as is evidently the case for c-erbB-2 and comedo DCIS.

Molecular and Cellular Markers of Risk

Specific genetic alterations occurring in human breast carcinomas are being identified with increasing frequency as molecular and immunological methods are applied to the study of human breast neoplasia. These alterations include the apparent inappropriate expression of growth factors and oncogenes as well as the loss of genetic suppressor alleles [34,35].

For example, the amplication of oncogenes HER-2/neu (c-erbB2), c-myc, and int-2 have been linked to human mammary cancer, while mutations in c-myc, and allelic deletions of c-rasHa, c-myc, or erb, as well as other oncogene alterations have also been associated with at least a portion of breast carcinomas [36-41]. Some of these alterations are present in a large fraction of mammary carcinomas. Up to 30% of mammary carcinomas, including *in situ* comedo type mammary carcinomas have been shown to have amplification, increased transcription and increased protein expression of the HER 2/neu (c-erbB2) oncogene [36-38]. Other frequently detected oncogene alterations are amplification of c-myc and allelic deletions of c-rasHa, present in approximately 20 and 30% of primary carcinomas respectively [39]. Allelic deletions of the c-rasHa and c-myc oncogenes [39], and variable expression of the estrogen induced pS2 gene [41] are other genetic alterations associated with human breast carcinoma. It is currently unknown if these same markers will serve to identify premalignancy. Many currently available measures of molecular biology, differentiation, etc. are available for study in human populations, but the path to further understanding of human carcinogenesis is not clear.

One area of current intense interest is the identification of a region on the short arm of the 17 chromosome which is linked to dense familial incidence of breast cancer as well as young age of occurrence [42]. This locus may also play a role in nonfamilial cases. Also, the tumor suppressor gene p53 may play an early role in the genesis of some breast cancers [43,44], probably usually by deletion or mutation.

The application of *in situ* methods (nucleic acid hybridization and immunohistochemistry) is permitting

the identification and analysis of altered expression of these same genes in lesions associated with increased risk. It is likely that the expression or alteration of specific genes in association with lesions of increased risk will provide additional prognostic information as well as provide insight into fundamental genetic events leading to the attainment of the malignant phenotype.

Summary

In summary, there are histopathologically identifiable lesions within the human breast which indicate later development of invasive breast cancer at an increased incidence over that of the general population. Many of these may be regarded as markers of increased risk because they are indicative of cancers presenting anywhere in either breast, while the non-comedo ductal carcinoma *in situ* lesions are unique in indicating a high likelihood of invasive disease at the same site of detection of the initial high risk lesion (Table 2).

Assessment of cancer risk, particularly with a view toward targeting strategies for prevention is a recent development. The future will see the garnering of more specific information about determinants of risk and their interaction with screening, prevention and therapeutic modalities. We are not more than a decade removed from a time when the question of malignancy in the breast was absolute, yes or no. Now special types of breast cancer are recognized that pose little threat to life, while some benign conditions indicate greatly increased risk of death of cancer. Comparison of premalignant determinants in other organ systems indicate that cytologic, histologic and metaplastic features may be more or less important in different organs. Their separate and combined analysis as predictors give a complex measure of tissue organization, which is often predictive of concurrent cancer and/or future cancer development.

Our major viewpoint in this discussion of premalignancy as it regards prevention is founded on the complexity of the carcinogenic process as well as the realization that in human populations it appears to be a stochastic process.

As discussed by Robb-Smith recently [45], there are many examples of multicentric cellular proliferation in which only a few foci become carcinomatous, thus arising in a background of hyperplasia. This is fundamental to the theory of progression of tumors to more malignant forms [4], and indicates that a solitary alteration in cellular dynamics is unlikely to explain malignant behavior.

Cancer is most frequently studied at mechanistic levels, now dominated by what is termed "molecular biology" and at other levels of biological organization that may be understood as: tissue, organs, organisms, and populations of organisms [46]. The promise of molecular biology to find ultimate explanations and causes is unexcelled. However, presently we need to relate the mechanistic or reductionist information to higher levels of biological phenomena within human populations [47]: a task falling within the area of epidemiology. The relationship of current basic science to epidemiology and the possible prevention of cancer has been reviewed by Muir in an enlightened way [48], but few promising and no certain target areas for a mechanistic solution are identified at this time.

In the human breast, minor examples of ductal carcinoma *in situ* is the lesions most closely fitting the model of a non-obligate, but frequent local precursor of invasive cancer. Most other anatomic indicators of increased cancer risk are best considered as general indicators or markers of risk because later cancer may occur elsewhere in the breast. The atypical hyperplasias are unfortunately weak practical models for intermediate endpoints of progression because of their rarity and focality in the breast.

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