

Cervical Cancer Prevention: More than Just a Pap in a Diverse Urban Community

Josephine R Fowler and Raja Sayegh*

Department of Obstetrics and Gynecology, Boston University, School of Medicine MA, USA

Abstract: Cervical cytologic screening and early management of abnormal pap smears played an important role in reducing invasive cervical cancer incidence and mortality over the past decades. Despite widely available cost effective screening for cervical cancer in the United States, women in lower socioeconomic groups and minorities continue to suffer from a higher incidence and mortality from cervical cancer and national goals have not been met. The biological, psychosocial, and cultural barriers that contribute to these disparities will be reviewed. This article also reviews current screening methodologies, treatment algorithms and newer developments that hold additional promise for the future of cervical cancer prevention.

INTRODUCTION

Cervical cancer is a largely preventable disease, yet it tragically remains the second most common cancer worldwide with over 500,000 new cases and 250,000 deaths annually [1]. In many regions of the world, e.g. Southeast Asia, East Africa, Melanesia, Central America, the Caribbean, South America, and Southern Africa, the incidence rate of cervical cancer approaches 30 cases per 100,000 women with high mortality rates from the disease. For the United States (US), the National Cancer Institute (NCI), and the American Cancer Society (ACS) estimate an overall incidence of 7.2 cases per 100,000 women with an overall mortality rate of 2.9 cases per 100,000, figures that are well above the healthy people 2010 goal of 2.0 cases per 100,000. Based on those figures approximately 12,800 new cases will be diagnosed in 2004 and 3,900 women will die from invasive disease [2].

Disparities in incidence of cervical cancer remain throughout the US. The incidence rate of cervical cancer for Hispanic, African American, and Asian/ Pacific Islander women is higher than that of non-Hispanic white women; 16.9, 12.4, 10.2 and 9.2 per 100,000 women respectively in 1996-2000 [3]. The highest age adjusted incidence rate of 43 per 100,000 is seen among Vietnamese women [4]. A number of studies in the US have shown that inner city immigrant and poor populations are not fully integrated in preventative and public healthcare initiatives. For example, only half of Asian American women have ever had routine check-ups, clinical breast exams, mammograms, and pap smears [5]. Among those inner city minority and migrant women, preinvasive cervical disease goes undiagnosed and untreated leading to a higher cervical cancer burden in those communities.

Although mortality from cervical cancer is rare for any group with prior screening and adequate follow-up, disparities in mortality from cervical cancer remain in the

US. African American women have twice the mortality rate for cervical cancer compared with non-Hispanic White women, (5.9 vs. 2.7 per 100,000 respectively in 1996 -2000) [6]. These differences are puzzling because a number of studies have shown that stage for stage; there are no racial or ethnic differences in cervical cancer survival [7]. This suggests that the reasons for the disparities lie mostly in the access to and quality of care and this has been underscored by a 2003 Institute of Medicine (IOM) report that found that African Americans with cervical cancer are more likely to go unstaged and receive no treatment [8].

SCREENING FOR PRE-INVASIVE DISEASE AND CANCER

The Pap Test

The Pap test, which relies on microscopic examination of the epithelial cells collected from the cervix, is the most effective and most widely used means of screening for precancerous and malignant lesions of the cervix [9]. Since screening was introduced in 1955 the incidence of invasive cervical cancer has decreased more than seventy-four percent [10]. The conventional Pap technique nonetheless is far from perfect and carries a 10-70% false-negative rate due to collection and processing errors necessitating that the test be performed annually for optimal performance. Recent studies have shown that more than half of the women diagnosed with invasive cervical cancer either have never had a pap smear, or their last smear was more than five years prior to diagnosis [11, 12]. More sensitive liquid pap collection and automated processing technologies have been recently introduced into clinical practice. Although these tests have improved sensitivity they suffer from lower specificity, which might lead to heightened anxiety among women who have no significant disease. There is also a cost concern; more false positive tests will mean an increased number of colposcopies for young women with no disease or with mild and self-limited transient HPV infections. The current challenge that is being pursued is to optimize the screening intervals for different risk groups allowing maximal

*Address correspondence to this author at the Department of Obstetrics and Gynecology, Boston University, School of Medicine MA, USA; E-mail: raja.sayegh@bmc.org

detection of significant disease, improved compliance, and overall cost reduction to the system.

Natural History of Human Papillomavirus Infection

Human papillomavirus (HPV), the most prevalent of sexually acquired infections accounts for nearly all cases of cervical cancer worldwide [13]. The relative risk of developing cervical cancer with HPV infection is 20-175 depending on the age of the patient and type of HPV [14]. It is important to emphasize however that the absolute risk of developing cervical cancer after an HPV infection, even with the high-risk types, is small. The majority of young healthy women under 30 who are so infected will have a transient self-limited infection with no sequelae. Moreover, the majority of those who develop preinvasive disease, or dysplasia, have spontaneous regression and resolution of the dysplasia. In the minority of women destined to progress to cervical cancer after HPV infection, there is a long preinvasive interval that is measured in years. Improving our knowledge about the natural history of HPV infection and of preinvasive diseases of the cervix is paramount to developing cost-effective screening strategies and management algorithms that minimize fear and anxiety and eliminate unnecessary and costly diagnostic and surgical interventions.

Current Screening Guidelines (Table 1)

Societal priorities, available technical and human resources, evolving scientific knowledge and population characteristics ultimately interact to determine the screening strategies and guidelines adopted by a particular country or society. An ideal screening program should target populations at most risk for disease, must be cost effective, must have good sensitivity and must be easy and practical to administer. The World Health Organization suggests that in the case of cervical cancer, the ideal target population for screening would be women aged 35 to 50 since these women are at highest risk for developing precancerous lesions and invasive cancer [15]. However, these recommendations may

not be useful in the inner cities of the US where the rates of cervical cancer in situ among African American women peak between ages 20-30, and starting to screen at age 35 might miss the opportunity to diagnose and treat preinvasive disease.

The American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG) and US Preventive Task Force (USPSTF) currently recommend beginning screening within three years of the onset of sexual intercourse or at age 21 whichever comes first. Their recommendations are quite similar with minor variations as noted in (Table 1). After age 30, less frequent screening is recommended in low risk women. The risk of precancerous or cancerous lesions in women with three normal paps is close to nil. Women with three negative screens may get screened every two to three years. Those with suspected deficiency in their immune system due to HIV, chronic steroid use, diethylstilbestrol exposure in utero, or post organ transplant, should continue annual screening. Women over 70 years of age with three or more consecutive negative cytology reports within a ten year period may discontinue annual screening as long as they are in good health and lack risk factors for lowered immune systems. The prevalence of invasive disease after hysterectomy for a benign disease is rare and therefore women who have had hysterectomy for benign disease no longer require annual pap smears [16].

HPV Types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 66, 68 and 70 are considered to be oncogenic or "high risk" for the development of cervical cancer [17]. Laboratory testing for the presence of 14 high risk types in the liquid pap medium is about 89.2% sensitive and has been available for clinical use for few years. Such HPV profiling as an adjunct to cytology has proven useful for clinical decision making in two situations; the pap test showing atypical squamous cells (ASCUS) and the woman over 30. In the former situation, which accounts for some 5-10% of all pap test results, the absence of oncogenic virus allows reassurance and triaging to annual repeat pap rather than to a painful, and costly

Table 1. Recommendations for Cervical Cancer Screening from American Cancer Society (ACS) and American College of Obstetrician and Gynecologists (ACOG) [18, 19]

Parameter	ACS-2002	ACOG-2003
Age to start	3 years after onset of sex. No later than age 21	Same
Age to stop	Age 70-if 3 consecutive normal paps and no history of DES, immunosuppression or dysplasia in past 10 years	No upper limit. Individualize and base on risk factors
Post Hysterectomy for benign disease	Not needed if hysterectomy for benign disease	Same
Screening interval up to age 30	Annually with conventional Pap or every two years with liquid cytology	Annual
Screening interval after age 30	If has three consecutive normal paps and no history of dysplasia, DES exposure or immunosuppression, can screen every 2-3 years	Same
HPV DNA testing and pap after age 30-screening interval	Test every three years if both negative. FDA approved	If both tests negative, repeat every three years

diagnostic work up. In the other half of ASCUS patients who test positive for an oncogenic virus, their risk of having a high grade dysplasia of the cervix is about 20% and should be referred for immediate colposcopy. In the woman over 30 who has a normal pap test, the absence of oncogenic virus also allows reassurance for the next three years and obviates the need for repeat pap testing annually (Table 1).

Barriers to Effective Screening

There are many reasons why 50% of women at risk in urban populations in the US do not partake in cervical cytologic screening. These include immigration status, language barriers, lack of affordable health insurance, lack of transportation, and fear of pain, lack of trust in the western medical establishment and a knowledge deficit about the importance and significance of the issue. Many of these issues require further evaluation in a larger context that tackles the big social issues of our time eg. Health insurance, poverty, education, race relations etc. The new screening technologies and algorithms mentioned above are not in themselves better than the conventional pap smear in reducing cancer incidence or mortality in these populations. However it is hoped that the cost savings realized from these technological advances can be invested in reaching, educating and screening those who have remained outside the system until now, and that is likely to reduce the disease burden and mortality from cervical cancer in the US.

DIAGNOSIS AND MANAGEMENT OF PRE-INVASIVE CERVICAL DISEASE

General Considerations

Colposcopy with targeted biopsies of the cervix and/or endocervical curettage is the usual next step when the pap test is abnormal. This is a resource intensive diagnostic test that requires expensive equipment and skilled clinical and laboratory personnel and is laden with fear and anxiety for the patient. It is thus important to triage patients into colposcopy in a way that maximizes diagnostic efficiency for high-grade lesions and minimizes negative colposcopies and those that diagnose mild disease as was discussed in previous sections of this manuscript. During pregnancy, colposcopy can be safely performed if needed. Biopsies and endocervical curettages are usually withheld due to increased risks of bleeding and rupture of membranes unless there is a strong colposcopic suspicion of invasive cancer. For all other cases, the procedure can be repeated postpartum taking advantage of the long interval required for disease progression.

Management of a biopsy proven dysplasia of the cervix depends on a number of factors and must be individualized. These factors include the severity of dysplasia, the presence of endocervical involvement, the patient's age, parity, and immune status, the patient-physician rapport as well as the clinician's risk tolerance and style of practice. The knowledge that most mild cervical dysplasias resolve spontaneously over a 1-2 year period should allow for expectant management in most such cases. Exceptions include mild dysplasia that involves the endocervix and those that persist after 1-2 years of expectant follow up. For moderate and severe dysplasia most clinicians favor ablative

treatment. This can be done using a cold knife, electro-excision procedure, or laser and is usually curative in 90-95% of cases. A full discussion of the pros and cons and indications for each approach is beyond the scope of this paper and the reader is referred to excellent monographs on this subject [20-22]. Intensive cytologic surveillance with or without follow up colposcopy is usually required in the year post treatment to make sure there is no recurrence or persistence of the disease. More recently post treatment surveillance solely with HPV testing has been entertained but this remains investigational.

Barriers to Effective Diagnosis and Management

Educating women about the risk factors associated with cervical cancer encourages empowerment and self-awareness of disease promoters. The educator should never assume the woman understands why she is being screened or that she understands the language related to cervical cancer and human papillomavirus. Educating women about HPV is sometimes synonymous with sex education for women. Discussing cervical cancer as a sexually transmitted disease may deter women from seeking primary screening or following up on abnormal cytology. There is conflicting data confirming modesty as a true barrier to receiving cervical cancer screening. Some women may want to take part in decision making while others prefer to have the provider suggest management options. African American women tend to view illness as a natural event caused by improper exposure to diet or external sources and accept it as "the will of God". They are more likely to want to "wait and see", seek family input or the input of clergy and desire inclusion in decision making [23, 24]. They are more empowered by being aware of the disease process and understanding why treatment is needed or how it will improve the outcome. Latino women tend to view illness as an improper balance between the internal and external forces. Decision making usually involves seeking the counsel of family preferably the eldest adult male. Latino women usually prefer like-gender providers [25]. Vietnamese women may view illness as an imbalance between body and nature, supernatural or spiritual where illness is the result of a curse, or as a result of "germ" contamination [26]. Concepts center on a harmonious relationship with the universe-guiding destiny. They may see hospital stay as a last resort before death [26-28]. Vietnamese women tend to be more modest about their bodies.

The very social, educational and cultural barriers that influence patient choice also influence the providers' recommendations and choices for management. A provider may chose to "err on the side of caution" and prescribe an aggressive treatment for mild dysplasia out of concern that the patient might not comply with expectant management and submit to intensive pap surveillance over 1-2 years. Given many physicians' limited experience with a multiethnic underserved population, cultural differences become a barrier to both patient compliance and physician's ability to educate and treat adequately, according to the IOM.

Future Considerations

Many centers are investigating a "see and treat" approach to managing preinvasive lesions. This approach utilizes

spectroscopic measurement of light reflectance by the cervix to assess the presence and severity of dysplasia on the spot and to offer ablative treatment in the same visit. If and when perfected, this is predicted to have a significant impact on compliance and cost because it eliminates the pain, wait and anxiety associated with the two step, two visit process involved in current diagnosis and management of dysplasia [29].

PREVENTION OF CERVICAL DYSPLASIA AND CANCER

Preventing HPV Transmission

There is very little one can do to reduce transmission of the ubiquitous HPV virus short of complete abstinence. Unlike other sexually transmitted infections, HPV transmission is not effectively blocked by the use of condoms [30, 31]. HPV can even be transmitted during non-penetrative sexual contact and this explains some cases of cervical HPV infection in young women who have not engaged in vaginal intercourse. Interestingly however oral-genital contact has not been associated with increased transmission risks [32]. Another interesting finding is that risk of HPV infection and cervical cancer is reduced in women whose partners are circumcised suggesting a significant health benefit to male circumcision, the mechanism of which is not fully understood [33].

Preventing HPV Infection

Researchers suggest that a vaccine aimed at preventing the most common HPV types (types 16 and 18) can have a major impact on eradicating cervical cancer. The ideal vaccine would have low costs, a long shelf life, and easy availability to those with the highest risk. One study [34] evaluating the utility of vaccinating adolescent girls 12 years of age at high risk for HPV suggest that we would need to vaccinate 600 girls to prevent one case of cervical cancer. Although this is more costly than current practices, more than 200,000 cases of HPV, 100,000 cases of SIL, and 3,000 cases of cervical cancer and 1,300 cases of cervical cancer death would be averted. When these same girls received a booster, the number of cases averted would be even greater. Vaccinating girls at age fifteen would result in a slightly

lower benefit. Identifying the ideal risk group and determining whether to vaccinate only pre-sexual adolescents versus those with high-risk behavior is yet to be determined. Other research is aimed at developing biomarkers to identify those at high risk for developing high-grade intraepithelial lesions and select them for vaccination.

The Role of Modifiable Cofactors

Since the advent of high risk HPV testing, two facts became apparent. Firstly, HPV infections are so common that almost all sexually active people become infected at some point in their lifetime. Secondly, most HPV positive women spontaneously become negative within 1-2 years due to the response of the immune system. It also became clear that long-term persistent infection with certain oncogenic types of HPV is necessary for high-grade cervical dysplasia and cancer to develop [35]. The possibility that modifiable "cofactors" are involved in the genesis of chronic persistent HPV infection has raised the hope that by modifying those factors one can prevent chronic HPV infection and consequently high-grade dysplasia and cancer. Possible cofactors are listed in (Table 2) and include infectious agents, hormonal factors, smoking, and nutritional deficiencies as well as social and behavioral factors. There is at this time however no strong scientific evidence that any of the interventions listed and referenced in the table below prevents cervical dysplasia and invasive cancer.

CLOSING REMARKS

Cervical Cancer is essentially a preventable disease, but the goal remains elusive particularly in the inner city where disparities continue to exist among minority underserved and impoverished multicultural populations. These disparities are multifactorial in origin and involve more than the traditional cost and access barriers to healthcare. It is hoped that a better understanding of the natural history of HPV infection coupled with new powerful screening technologies will allow the development of cost effective screening strategies that target high risk populations in the inner cities. It is also hoped that such approaches will free up financial resources that could be used for culturally competent educational and public health campaigns aimed at drawing segments of

Table 2. Modifiable Cofactors in Promoting Cervical Dysplasia and Cancer

Modifiable Cofactor	Intervention	Result
STD reduction [36]	Education regarding safe sex practices, sexual partner reduction, abstinence education in young women	Reduce STD transmission Limit HPV infections Reduce Cervical Cancer incidence.
Micronutrients [37]	Eat a well balanced meal Increase Fruits and vegetables. Vitamin supplements.	Reduce overall cancer risk
Cigarette smoking [38, 39]	Smoking cessation	Reduce overall disease risk Reduce cervical intraepithelial neoplasia Reduce cancer risk
Oral contraceptives [40]	Chose alternatives	Uncertain benefit

society that have traditionally chosen not to take advantage of what modern medicine has to offer. Cultural competency of providers should include not only epidemiology, screening and follow-up guidelines, but also instruction in health beliefs and customs of the target populations. Providers must learn how to deliver sensitive "cancer" and "sex" education in a manner that encourages participation in preventive behavior and preventive care. It is only then that the medical establishment can make a quantum leap and a major impact on relieving the burden of cervical cancer in the inner cities.

REFERENCES

- [1] GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide, Version 1.0. IARC Cancer Base No. 5. Lyon, IARC Press, 2001.
- [2] American Cancer Society: Cancer Facts and Figures 2004. Atlanta Ga. American Cancer Society 2004.
- [3] American Cancer Society: Cancer Facts and Figures 2004. Atlanta Ga. American Cancer Society 2004.
- [4] Miller BA, Kolonel LN, Bernstein L, *et al.* (eds) Racial/ Ethnic Patterns of Cancer in the United States 1988-1992, National Cancer Institute. NIH Pub. No. 96-4104. Bethesda, MD, 1996.
- [5] Pham CT, McPhee SJ. Knowledge, attitudes, and practices of breast and cervical cancer screening among Vietnamese women. *J. Cancer Educ* 1992; 7: 305-310.
- [6] American Cancer Society: Cancer Facts and Figures 2004. Atlanta Ga. American Cancer Society 2004.
- [7] Farley JH, Hines JF, Taylor RR, *et al.* Equal care ensures equal survival for African-American women with cervical carcinoma. *Cancer (Phila.)* 2001; 91: 869-873.
- [8] Merrill RM, Merrill AV, Mayer LS. Factors associated with no surgery or radiation therapy for invasive cervical cancer in Black and White women. *Ethn Dis* 2000; 10: 248-256.
- [9] NIH Consensus Statement on Cervical Cancer. November 15, 1996, AFP.
- [10] American Cancer Society: Cancer Facts and Figures 2004. Atlanta Ga. American Cancer Society 2004.
- [11] Spitzer M. Cervical Screening Adjuncts: Recent Advances. *Am J Obstet Gynecol* 1998; 179: 544-56.
- [12] Sawaya GF, Grimes DA. New Technologies In Cervical Cytology Screen A Word Of Caution, *Obstet Gynecol* 1999; 94: 307-10.
- [13] National Institutes of Health (NIH). Consensus Development Conference Statement 1996.
- [14] Wright Jr. T. Part 2. Human Papillomavirus and Cervical Disease. Update in Gynecology from the ACOG Annual Clinical Meeting. *Medscape Women's health* 2001; 6(1).
- [15] Sankaranarayanan R, Budukh AM, Rajkumar R. Effective Screening Programmes for cervical cancer in low and middle income developing countries. *Bulletin of World Health Organization* 2001; 79.
- [16] Saslow D, Runowicz CD, Solomon D, *et al.* American Cancer Society guideline for the early detection of cervical neoplasia and cancer. *CA Cancer J Clin* 2002; 52: 342-360
- [17] Burd EM. Human Papillomavirus and Cervical Cancer. *Clin Microbiol Rev* 2003; 16(1): 1-17.
- [18] Saslow D, Runowicz CD, Solomon D, *et al.* American cancer Society Guideline for Early detection of Cervical Neoplasia and Cancer. *CA Cancer J Clin* 2002; 52: 342-362.
- [19] American College of Obstetricians and Gynecologists. Guidelines for Women's Health Care. 2nd ed. Washington, DC: ACOG 2002; 121-134, 140-141.
- [20] Wright, TC Jr, Cox, JT, Massad, LS, *et al.* 2001 consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003; 189: 295-304.
- [21] Management of women with biopsy confirmed cervical intraepithelial lesions. www.asccp.org/pdfs/consensus/algorithms_hist.pdf [Accessed 2004 Oct 15].
- [22] Hunter, MI, Holschneider, CH: Cervical intraepithelial neoplasia: Management. www.uptodateonline.com. October 2003 edition.
- [23] Diversity and Health Care Resource Center. Culture-Sensitive Health Care: African Americans. Copyright 1999.
- [24] Locks S and Boateng LA. Black/African Americans. In Lipson JG, Dibble SL and Minarik PA, eds. (1996). *Culture and Nursing Care: A Pocket Guide*. San Francisco, CA: University of California San Francisco Nursing Press.
- [25] Scrimshaw SCM, Zambrana R, Dunkel-Schetter C. Issues in Latino women's health: myths and challenges. In: Ruzek S, Oleson V, Clarke A, eds. *Women's Health: Complexities and Differences*. Columbus, OH: Ohio State University Press 1996.
- [26] <http://www.diversityinhealth.com/regions/asia/vietnamese.htm> [Accessed Oct 2004].
- [27] Buchwald D, Panwala S, and Hooton TM: The Use of Traditional Health Practices by Southeast Asian refugees in a Primary Care Clinic. *West J Med* 1992; 156(5): 507- 511.
- [28] Uba L: Cultural Barriers to Health Care for Southeast Asian Refugees. *Pub Health Reports* 1992; 107(5): 544-549.
- [29] Wright TC Jr, Menton M, Myrtle JF, Chow C, Singer A. Visualization techniques (colposcopy, direct visual inspection, and spectroscopic and other visual methods). Summary of task force 7. *Acta Cytol* 2002; 46(5): 793-800.
- [30] "Condom Sense: Is It Enough?" Medical Institute for Sexual health, June 1997.
- [31] "HPV and cervical Dysplasia patient Information", Louisiana State University Medical Center Midland family Physicians-LSUMC family Medicine patient Education Home page, 1996, <http://lib-sh.lsumc.edu/fammed/pted/ppvmid.html>. [Accessed Oct 2004].
- [32] Winer RL, Lee SK, Hughes JP, Adams DG, Kiviat NB, Koutsky LA. Genital Human papillomavirus Infection: Incidence and Risk Factors in a Cohort of Female University Students. *Am J Epidemiol* 2003; 157: 218-226.
- [33] Castellsague X, Bosch FX, Munoz N, *et al.* Male Circumcision, Penile Human Papillomavirus Infection, and cervical Cancer in Female Partners. *N Engl J Med* 2002; 346(15): 1105-12.
- [34] Sanders GD, Taira AV. Cost-Effectiveness of a Potential Vaccine for Human Papillomavirus. *Emerg Infect Dis* 2003; 9(1): 37-48.
- [35] Kjaer SK, van de Brule AJ, Paull G, *et al.* Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow-up. *BMJ* 2002; 325(7364): 572.
- [36] Shepherd J, Weston R, Peersman G, Napuli IZ. Interventions for encouraging sexual lifestyles and behaviours intended to prevent cervical cancer. *Cochrane Rev Abstract* 2004.
- [37] Yeo AS, Schiff MA, Montoya G, Masuk M, van Asselt-King L, Becker TM. Serum micronutrients and cervical dysplasia in Southwestern American Indian women. *Nutr Cancer* 2000; 38(2): 141-150.
- [38] Luesley, D, Blomfield P, Dunn J, Shafi M, Chenoy R, Buxton J. Cigarette smoking and histological outcome in women with mildly dyskaryotic cervical smears. *Br J Obstet Gynaecol* 1994; 101(1): 49-52.
- [39] Daly SF, Doyle M, English J, Turner M, Clinch J, Prendiville W. Can the number of cigarettes smoked predict high-grade cervical intraepithelial neoplasia among women with mildly abnormal cervical smears? *Am J Obstet Gynecol* 1998; 179(2): 399-402.
- [40] Moreno V, Bosch X, Munoz N, *et al.* Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. *Lancet* 2002; 359(9312): 1085-1092.