Gynecologic Oncology 154 (2019) 3–7

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Historical Perspective

Pathway to the Papanicolaou smear: The development of cervical cytology in twentieth-century America and implications in the present day

Alexa L. Swailes [a,*], Carrie E. Hossler [a], Joshua P. Kesterson [b]

[a] Division of Women's Health, Department of Obstetrics and Gynecology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, United States of America
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Penn State Health Milton S. Hershey Medical Center, Hershey, PA, United States of America

HIGHLIGHTS

- Papanicolaou first described the Pap smear in 1928. His findings were not recognized by the medical community until 1941.
- The 1941 re-publication of the Pap method spurred epidemiologic studies and screening protocols for cervical cancer.
- In 1983, human papillomavirus was identified as the causal agent for cervical dysplasia by Harald zur Hausen.
- Recent developments in cervical cytology include use of liquid-based cytology and HPV genotyping.

ARTICLE INFO

Article history:
Received 9 February 2019
Received in revised form 24 March 2019
Accepted 2 April 2019
Available online 15 April 2019

Keywords:
Cervical cancer
Papanicolaou
Cervical cytology
Exfoliative cytology

ABSTRACT

George Papanicolaou, a Greek immigrant and cytopathologist, was responsible for what is now colloquially known as the "Pap smear"—undoubtedly one of the greatest advances in medicine and public health of the last century. However, his landmark research on the development of cervical cytology for the detection of precancerous lesions of the cervix ("New Cancer Diagnosis," 1928) made a rather inauspicious debut in an unlikely venue: John Harvey Kellogg's Third Race Betterment Conference—a meeting devoted to the furtherance of the concept and implementation of eugenics. Herein, we discuss the stark juxtaposition of Papanicolaou's landmark discovery amid the pseudoscience of the third Race Betterment Conference. We discuss the latency of Papnicolaou's discovery–its potential implications unrealized–until co-publication with Herbert Traut, which catapulted Papanicolaou's research to the scientific foreground. This gave rise to public health initiatives aimed at establishing the Pap smear as a screening tool. We further delineate the progress made in recent decades with the identification of HPV as the etiological agent for cervical cancer, and the subsequent development of the HPV vaccine, and discuss ongoing research in the present day. In this way, we hope to provide a background and historical context for the development of the Pap smear.

1. Introduction

In 1928, George Papanicolaou—a Greek immigrant and cytopathologist—presented "New Cancer Diagnosis," a short manuscript with a rather non-descript title, at the Third Race Betterment Conference in Battle Creek, Michigan [1]. At the time, little was known about the epidemiology, natural history, or even pathologic findings of cervical cancer, though undeniably a scourge affecting young women.

In "New Cancer Diagnosis,"—nestled among presentations such as "Who Outbreeds Whom?" by Edward Ross, a professor of Sociology at the University of Wisconsin, "The Sterilization of Feeble Minded in Michigan," by Dr. H.E. Randall, president of the Michigan State Medical Society, and "The Menace of the Melting Pot Myth," by Albert Johnson, U.S. Representative and Chairman of the Committee on Immigration and Naturalization [1]— Papanicolaou described his theory that malignant cells, taken from a sampling of vaginal fluid, bore certain identifiable characteristics that distinguished them from other benign pathologies. He described findings now readily recognized as hallmarks of dysplasia and malignancy, including abnormal size of cellular nuclei, dense and fragmented chromatin, and vacuolar cytoplasm. He further remarked on the mononuclear leukocytic reaction in response to these starkly abnormal cells [2].

* Corresponding author at: 500 University Dr., MC H103, Hershey, PA 17033, United States of America.
E-mail address: aswailes@pennstatehealth.psu.edu (A.L. Swailes).

https://doi.org/10.1016/j.ygyno.2019.04.004
0090-8258/

With parsimonious economy of words, he enumerated his findings in four key points:

> *First: we have a new diagnostic method for certain malignant tumors, especially of the female genital tract. Second: the methods and the technique used are very simple ones and can easily be applied in every case. Third: the recognition of malignancy is based not only on the presence of malignant cells, but also on the reaction of the organism itself. Fourth: we have a better understanding of the situation in a cancer case, and we may have some help in analyzing the cancer problem in the future* [2].

Perhaps Papanicolaou himself was unaware of the magnitude of his discovery. Yet, while the contents of his manuscript heralded a new age in cancer screening, they went unappreciated in their significance for over a decade.

2. Background

2.1. George Papanicolaou

George Papanicolaou was born in 1883 in Kymi, on the island of Euboea in Greece—a small town located on the "balcony of the Aegean sea," in a region renowned for its production of wine, olives, and figs. George's father, Nicolaos Papanicolaou, was a physician, mayor of Kymi, and Greek Member of Parliament. As a young man, George Papanicolaou fostered many interests, including philosophy, French, and classical violin. At the age of 11, he left Kymi to pursue his secondary education in Athens [3].

In 1898, he enrolled in the University of Athens, following in his father's footsteps to undertake the study of medicine. Upon his graduation *summa cum laude* in 1904, he commenced two years of compulsory medical service in the Greek army. After his discharge in 1906, he was encouraged by his father to return home to practice in Kymi, or to continue his service as a military doctor. For a brief period of time, George complied with his father's wishes, returning home to practice medicine in an effort to better situate himself financially. However, underwhelmed by the opportunities available to him as a physician in Greece, he decided to go abroad in pursuit of further study [3–5]. Many years later, he would remark, "I finally decided to leave Greece because, among other things, I was greatly influenced by my father's fate – the fate of a genius confined in a restricted environment." [3]

In late 1907, Papanicolaou made his way to Germany with his father's blessing. He traveled first to Munich, where he began learning the German language and adapting to German culture. Then, following eminent biologist Ernst Haeckel, he made his way to Jena, where he enrolled in the University of Jena to study Comparative Zoology. Finding that he was not obtaining the basis he needed for his future work, after 6 months, he relocated to Freiburg to study under evolutionary theorist August Weisman, the founder of germ plasm theory. After 6 months in Freiburg, Papanicolaou again uprooted, this time returning to Munich, where he would study under Richard Hertwig (discoverer of the zygote) and Richard Goldschmidt at the University of Munich. In 1910, he successfully defended his doctoral thesis "*On the terms of sexual differentiation of the Daphnides*," and received his Ph.D. in Zoology [3].

Papanicolaou returned briefly to Kymi upon his graduation, after 3 years without seeing his family. During this trip, he made the acquaintance of Andromache (Mary) Mavroyeni, and in September 1910, the couple was married in a small ceremony in Athens. Soon after their wedding, George and Mary set off for France to visit research centers throughout the country. From France, they traveled to Monaco where George was offered a position by Prince Albert I as a physiologist on board his research ship. In July 1911, the ship disembarked, traveling to Gibraltar, the Canary Islands, Madeira, and the Azores, returning to Monaco in September 1911. Thereafter, George and Mary returned to Greece following the news of his mother's death. While in Greece, the Balkan War erupted, and George was called to duty as a member of the active reserves. He served until 1913, meeting many Greek-Americans along the way, who convinced him of the need for young scientists in the United States. In September 1913, with $250 to their names, George and Mary Papanicolaou left Kymi for New York City. [3–6]

Upon his arrival to the United States, George Papanicolaou spoke limited English and was quite without funds. He and Mary obtained employment in a department store. Over-qualified and ill-suited to his work as a carpet salesman, he sought a meeting with Dr. Thomas Morgan, a well-known professor of Biology at Columbia University to ask for assistance in obtaining a position within his field. Morgan (having cited Papanicolaou's doctoral work extensively in his textbook *Heredity and Sex)* immediately complied, issuing requests to many contacts, including Dr. William Elser, director of the Department of Pathology at the New York Hospital, who offered Papanicolaou a job as a laboratory assistant. A short while later, in 1914, Elser recommended him to Dr. Charles Stockard, professor of Anatomy at Cornell University Medical College, for a position in the Department of Anatomy [3–5].

Upon his arrival, he began his research on the estrous cycle of guinea pigs—an animal commonly used for breeding experiments and research on sexual conditions, which were poorly understood at the time [5]. In 1917, jointly with Charles Stockard, Papanicolaou published "The Existence of a Typical Oestrous Cycle in the Guinea Pig—With a Study of its Histological and Physiological Changes" in the journal *Science*. [7] Papanicolaou further theorized that his findings of cellular changes dependent on the estrous cycle could ultimately be extrapolated to other species, and, indeed, humans. His first human subject was his wife, in whom he observed cyclic changes in vaginal cytology analogous to those found in guinea pigs. In 1925, he began a study of vaginal smears obtained from staff volunteers at the New York Women's Hospital. An incidental finding of uterine cancer led him to recruit more women with the condition, and culminated in his landmark findings presented in Battle Creek, Michigan [4,5].

2.2. John Harvey Kellogg

John Harvey Kellogg was born in 1852 in Tyrone, Michigan to John Preston and Ann Kellogg, fervent Protestant Christians devoted to healthy living and austere religiosity. When J.H. Kellogg was four years old, his family moved to Battle Creek, Michigan as part of a small community of devoted followers from which the Seventh-Day Adventist denomination would spring [8]. In 1863, the Seventh-Day Adventist church was formally founded in Battle Creek. Two years later, Ellen White, the community's spiritual guide, inspired by a vision, set about a mission to "speak against intemperance of every kind—intemperance in working, in eating, in drinking, in drugging" and "provide a home for the afflicted and those who wish to learn how to take care of their own bodies that they may prevent sickness." [9] With seed money provided by John Preston Kellogg, the Seventh-Day Adventist Church founded the Western Health Reform Institute, inspired by the vision of Ellen White [9].

During this time, John Harvey Kellogg completed his secondary education, and initially enrolled in the Michigan State Normal College in Ypsilanti, Michigan with the intention of becoming a teacher. However, under pressure from his family, he was persuaded in 1872 to forgo his training as a teacher and pursue the study of medicine with the ultimate goal of returning to staff the Western Health Reform Institute. Thus, J.H. Kellogg traveled to New Jersey, to Dr. Russell Trall's Hygieo-Therapeutic College, where he undertook the study of the impact of behaviors (diet, exercise, water consumption, *etc.*) on health. After six months, upon completion of his studies in New Jersey, he returned to Michigan to the University Medical School in Ann Arbor. Receiving a grant from Ellen White and her husband, he went on to complete his medical degree at the Bellevue Hospital Medical School in New York. Upon his graduation in 1875, he returned to Michigan and accepted a position

as a staff physician at the Western Health Reform Institute. In 1876, he was appointed medical superintendent [8,10]. In 1877, determined to rescue the Institute from its legacy of financial mismanagement and subpar medical care, J.H. Kellogg rebranded it as the Battle Creek Sanitarium—the birthplace of Kellogg's Corn Flakes™.

Despite dedicating the larger portion of his life and career to the health of others, along the course of his studies, John Harvey Kellogg began to ascribe to the teachings of Charles Davenport, a prominent 20th century eugenicist. Thereafter, Kellogg's research began to turn toward the nefarious beliefs of "race degeneracy" [11]—leading him to found the Race Betterment Foundation jointly with Davenport in 1906. The first iteration of the Race Betterment Conference took place in 1911. In 1913, he presented before the meeting of the American Public Health Association a paper entitled "Relation of Public Health to Race Degeneracy," in which he lamented the "remarkable depreciation in racial vitality and stamina" in the United States [11]. He devoted the next years of his life to solving the problems of "race degeneracy," soliciting the research of like-minded pseudoscientists, and forming extensive conferences on how to improve the health of the nation. The role of the immigrant in the degeneration of American society was not overlooked at these conferences. Thus, it is curious indeed how George Papanicolaou, a humble Greek immigrant, was invited to the Third Race Betterment Conference to first present his research.

3. Re-emergence of the Pap Smear

After his 1928 presentation, "New Cancer Diagnosis," at the Third Race Betterment Conference, George Papanicolaou continued his research without much fanfare and with no significant clinical implementation of his findings. It was not until over a decade later that he began collaboration with Herbert Traut, a pathologist at Cornell University, with whom he worked on optimizing the vaginal smear technique and fixation of samples. Their work largely focused on characterizing malignant cells and crafting a manuscript to describe their findings. In 1941, Papanicolaou and Traut published "The Diagnostic Value of Vaginal Smears in Carcinoma of the Uterus" in the American Journal of Obstetrics and Gynecology. [12]

With greater prowess of prose than that originally offered in Papanicolaou's 1928 publication, Papanicolaou and Traut set the stage for their research by lamenting the fact that until cervical cancer was better understood, and early diagnosis feasible, there could be no hope for increasing survival for the young women afflicted. They went on to underscore that uterine carcinomas are exfoliative lesions, and thus, malignant cells can become dislodged and present in the vagina. They further described eight characteristics of malignant cells that are pathognomonic of carcinomatous changes: 1) atypical size of nuclei with granular chromatin, 2) hyperchromatic nuclei, 3) aberrant indentations or bulging nuclei, 4) multinucleated cells, 5) nuclei in premitotic or mitotic phase, 6) dense cytosplasm, 7) cytoplasmic vacuoles, and 8) histiocytosis of vaginal fluid [12].

In their discussion, they spoke of the ease of use of the Papanicolaou smear, stating that "requirements of diagnosis are not above the powers of any trained cytologist after these have had adequate training and sufficient experience." They acknowledged their lack of statistical significance with few specimens, but offered their assurance that screening via the Papanicolaou method resulted in a high percentage of correct diagnoses when confirmed by tissue biopsy. They finished with the compelling statement that "we hope that [this technique may] eventually be applied widely so that the incipient phases of the disease may come more promptly within the range of our modern methods of treatment." [12]

Contrary to the 1928 publication by Papanicolaou, the 1941 coauthored manuscript made an earnest plea for the vaginal smear. It detailed the pervasiveness of cervical cancer in modern society. It provided an achievable means by which to screen, and explicit instruction and reassurance to those hesitant to learn a new pathologic technique. Furthermore, it reached a wide audience with a compelling message. In short, it achieved everything that the original manuscript did not.

Shortly thereafter, in 1943, Papanicolaou and Traut published "Cancer of the Uterus: the Vaginal Smear in its Diagnosis" in *California and Western Medicine*. This publication contained largely the same information as the 1941 manuscript, but expanded upon it by quantifying the effects of the vaginal smear when compared to biopsy. In it, Papanicolaou and Traut detailed 193 cases of carcinoma of the uterus, of which 126 were either squamous cell or adenocarcinoma of the cervix. The vaginal smear was able to detect all but 1.3% of cases of biopsy-confirmed cancer, and those unable to be detected were due to brisk bleeding and post-radiation effect—suggesting the high sensitivity of the vaginal smear as a screening tool. Papanicolaou and Traut further underscored the fact that 13 cases of adenocarcinoma of the uterus were discovered that were previously undetected by clinical means. They concluded with the compelling statement that "it is clear therefore, that the vaginal smear is the best of any single available method. And that as far as early carcinoma of the cervix and silent carcinoma of the fundus are concerned, it is far superior to biopsy," [13] thus outlining a role for the Pap smear as a screening test, laying the groundwork for the public health efforts over the next decade.

In 1946, Papanicolaou published an update to the progress of the vaginal smear entitled "Diagnostic Value of Exfoliated Cells from Cancerous Tissues" in the Journal of the American Medical Association. In this manuscript, he detailed the studies performed by Joe Vincent Meigs at Harvard Medical School, wherein 1015 cases of uterine and cervical cancer were identified by vaginal smear. Papanicolaou further cited the studies of Charlotte Jones, Thomas Neustaedter, and Locke Mackenzie of the Post-Graduate Hospital of New York and J. Earnest Ayre of the Royal Victoria Hospital in Montreal, whose studies corroborated his findings. However, more interestingly, in this manuscript, Papanicolaou offered a rare introspection into the failure of his original publication in 1928 to cultivate interest within the scientific community, stating:

> *"Despite the early recognition of the fact that malignant tumors of the uterus could be diagnosed by the vaginal smear test and the conclusive evidence offered by a large number of cases, I must admit that I failed utterly in arousing the interest of clinical men in the potentialities of this diagnostic method and in gaining their confidence. […] I had given only a short and incomplete account of my observations relating to cancer diagnosis. [..] Then, not being a pathologist, I had been handicapped by my inadequate pathologic training, which prevented me from grasping the full significance of certain deviations from the normal cell pattern and their relationship to the different types of neoplasms."* [14]

4. Epidemiologic groundwork for the study of cervical cancer

Given the vaginal smear's role in detecting cervical cancer in its incipient stages, physicians and scientists alike soon began to seek epidemiologic data so as to better elucidate its clinical course and impact. In 1954, John Dunn et al. published "Uterine Cancer Morbidity Data: Memphis and Shelby County Tennessee 1950-1951" in Public Health Reports. In this manuscript, the authors endeavored to elucidate uterine cancer morbidity rates as well as determine the relationship of carcinoma *in situ* of the cervix to invasive cervical cancer. [15]

Of 164,325 women over the age of 20 residing in the city of Memphis and Shelby County, 970 cases of uterine cancer were recorded, comprising 883 invasive cases (687 invasive to the cervix, 127 invasive to the fundus, and 69 "other"), and 87 cases of carcinoma *in situ* of the cervix. Data were obtained retrospectively from physician and medical facility records as well as death certificates. In this review, the authors found that cervical cancer was 1.7 times more common in non-white individuals as it was in whites. They likewise found a sharp uptick in diagnoses after the age of 60 [15].

Though the data gleaned from this study and resultant statistical analyses were initially rudimentary, they provided the underpinnings for our understanding of cervical cancer from a pathophysiologic and epidemiologic perspective. The conclusions the authors drew, though elementary, were essential:

> *Present evidence suggests that cervical cancer, when symptomatically or clinically evident, as it usually is when diagnosed, has already been present many months or years. Therefore, a female population contains many individuals at all times with cervical cancer in various stages of development.[…] If carcinoma in situ of the cervix is the usual precursor of invasive carcinoma of the cervix, then this will be the new stage of recognition of the disease in the population being searched periodically for cervical cancer by exfoliative cytology screening* [15].

Shortly after the previous study was published, the National Cancer Institute offered funding for a mass screening program in Memphis and Shelby County, Tennessee. Preliminary data from this screening was reported in *CA: a Cancer Journal for Clinicians* in *1955*. In this brief report, Erickson categorized the results of vaginal smears into invasive disease, non-invasive disease (carcinoma *in situ*), and atypical/inconclusive results. He described a false positive and false negative rate below 0.1% as confirmed by biopsy, and further stated that 60% of biopsy-proven invasive and non-invasive cancers were asymptomatic at the time of their detection, offering further support for the role for the vaginal smear as a screening tool. [16]

The full-length report of the Memphis and Shelby county screening programs was published by John Dunn in 1958 in the American Journal of Public Health. Dunn and colleagues named two specific aims of the paper: to determine the utility of the vaginal smear in mass screening, and to study the relationship between carcinoma *in situ* of the cervix and invasive cervical cancer. With regard to the natural history of cervical cancer, Dunn states that the time from onset of invasive disease to diagnosis due to symptomatology was 4.1 years in white patients and 3.7 years in black patients. He deduced that the time of progression from carcinoma *in situ* to frank invasion was 5 years in white patients and 4 years in black patients. Beyond elucidating the natural history of cervical cancer, with this finding, Dunn may have described for the first time, the role of demographics and socioeconomic status in cancer biology. [17]

This paper was of landmark importance for a number of reasons. First, Dunn argued that carcinoma *in situ* was a likely precursor lesion to invasive cervical cancer. Further, he raised the hypothesis that some pre-cancerous lesions exist (likely the atypical smears) that may spontaneously regress. Perhaps most importantly, however, he delineated the role of the vaginal smear in identifying not only asymptomatic invasive cancer, but pre-invasive lesions, and that *via* intervention, avoiding the progression to cancer was possible. He concluded by stating that "periodic cytological examination […] offers considerable advantage in the earlier discovery of invasive cervical cancer," paving the way for the vaginal smear to be included in standard screening for women [17].

In 1956, the National Cancer Institute began its funding of another cervical cancer detection project in Jefferson County, Kentucky in conjunction with the University of Louisville School Of Medicine. This study ("Control of Cervical Cancer – Preliminary Report on Community Program") was published in the Journal of the American Medical Association in 1962. The investigators introduced the vaginal smear into routine physicals for approximately 20,000 women. In this large-scale study, Cristopherson et al. identified an alternate pathologic category of disease: cervical dysplasia. Though they found that diagnosis of dysplasia *versus* carcinoma *in situ* varied significantly from pathologist to pathologist, the authors hypothesized that dysplasia was a precursor of carcinoma *in situ*, but that not all cases progress, given the high rates of detection of cervical dysplasia compared to carcinoma *in situ* or frankly invasive lesions. Furthermore, the authors investigated the differential socioeconomic burden of disease by categorizing their participants as private patients, patients of a charity hospital, or women working in industry, finding that lower socioeconomic class was predictive of increased incidence of cervical cancer. In a striking endorsement of the role of the vaginal smear in routine well-woman care, Cristopherson et al. concluded by prophetically stating "it is suggested that deaths from cervical cancer could virtually be eliminated if all women had yearly cervical cell examinations." [18]

5. The search for an etiological agent for cervical cancer

With the pronounced push for the integration of the vaginal smear into the annual physical following the publication of Cristopherson's manuscript in 1962, the remainder of the 1960s marked an era in which the scientific community eagerly sought information regarding the etiology of cervical cancer. A sexually transmitted vector as a causative agent in cervical cancer had long been postulated, beginning early in the 20th century, with hypotheses that numerous sexually transmitted bacterial infections were the culprits. [19] As time went on, the scientific community refocused on the possibility of a viral vector as an etiologic agent for cervical cancer.

By the 1960s, it was well known that viruses could serve as causative agents in various cancers. In 1966, the Nobel Prize in Physiology or Medicine was awarded to Peyton Rous for his 1911 work elucidating the role of the Rous sarcoma virus in the development of avian malignancy [20]. He further studied rabbit papilloma virus, demonstrating that viruses were able to incorporate their own genetic code into that of their hosts [19,21].

In 1974, Harald zur Hausen began to investigate the role of viruses in the development of cervical cancer. He initially suspected HSV-2 as the causative agent, in keeping with the prevailing scientific opinion of the time. However, this was not borne out in genetic sequencing of cervical cancer tumor tissue [22,23]. In 1977, he published his landmark paper "Human Papillomaviruses and their possible role in squamous cell carcinomas" in Current Topics in Microbiology and Immunology, in which he discussed the role of HPV in genital warts and squamous cell carcinomas of the vulva, cervix, penis, and anus [24]. Shortly thereafter, in 1983, Grissmann and zur Hausen were able to demonstrate the presence of HPV-16 DNA in the host genome in tumor tissue *via* genetic sequencing. In 1984, they were able to demonstrate the presence of HPV-18 [25,26]. With the identification of an etiological agent, zur Hausen introduced the notion that cervical cancer could not only be cured, but could potentially be prevented. Indeed, 2006 saw the introduction and Food and Drug Administration approval of the Gardasil vaccine for the prevention of infection with HPV—the first vaccine to ever have the primary aim of preventing cancer [27]. In 2008, zur Hausen was awarded the Nobel Prize in Physiology or Medicine for his discovery [25].

6. Recent advances

Nearly a century after its discovery, the basic premise of the Pap smear remains largely the same—exfoliative cytology. In 1988, the Bethesda System was implemented in order to standardize reporting of cytology results. In 1996, liquid-based cytology was introduced, with the aim of improving detection of abnormal cellular morphology [28]. While the effectiveness of liquid-based cytology in increasing detection rates remains a matter of debate [29], it has allowed for the development of molecular-based HPV genotyping in conjunction with cytology. Genotyping, in turn, has allowed for risk-stratification of abnormal findings. In 2001, the American Society of Colposcopy and Cervical Pathology (ASCCP) issued evidence-based guidelines for the management of patients with abnormal cytology. Current research focuses on the analysis of immunomarkers in conjunction with cytology and HPV genotyping, as well as use of HPV testing as a primary screening tool [30].

Yet, despite advances made in developed countries, it cannot go without mention that worldwide, cervical cancer remains the leading gynecologic malignancy and the fourth most common malignancy

affecting women, with 570,000 new cases diagnosed in 2018 [31] and estimated deaths per year numbering more than 300,000 [32]. Of these, 90% of all cervical cancer deaths occur in low- or middle-income countries—many of which have no standardized screening programs [31]. The challenge remains of developing low-cost, universal screening modalities that can be implemented in low-resource environments. Recent efforts have focused on visual inspection with acetic acid (*VIA*) and rapid HPV testing as potential alternatives to standard cytology [33].

7. Conclusion

The role of what is now known colloquially as the Pap smear in preventing and detecting cervical cancer had its origins in a seemingly unlikely hero and an unlikely setting. George Papanicolaou—exactly the kind of "racial degenerate" and "menace to the melting pot" [1] that John Harvey Kellogg hoped to breed out of American society—arrived in the United States with few possessions and no professional standing. Yet through perseverance, dedication, and a certain degree of serendipity, he humbly became a scientific giant. His work was expanded upon by those with similar tenacity, giving rise to the first vaccine with the capability of preventing cancer. A great debt is owed to those who look upon their incidental findings with so critical an eye and espouse a willingness to challenge the prevailing scientific dogma of their time.

Conflict of interest statement

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

Author contributions

Conception and Design – Kesterson
Collection/Assembly of Data – Swailes, Hossler, Kesterson
Manuscript Writing – Swailes, Kesterson
Final Approval of Manuscript – Swailes, Hossler, Kesterson
Accountable for All Aspects – Swailes, Hossler, Kesterson

References

[1] National Conference on Race Betterment RBf. Proceedings of the Third Race Betterment Conference, January 2–6, 1928. , Race Betterment Foundation, Battle Creek, MI, 1928.
[2] G.N. Papanicolaou, New cancer diagnosis, Proceedings of the Third Race Betterment Conference 1928, pp. 528–534.
[3] M. Papanicolaou-Kokkori, G.N. Papanicolaou, M.D., Ph.D.: Life and Career: The Way to the Pap Test, Hellenic Medical Society of New York, New York, NY., 2008
[4] S.P. Michalas, The Pap test: George N. Papanicolaou (1883-1962). A screening test for the prevention of cancer of uterine cervix, Eur. J. Obstet. Gynecol. Reprod. Biol. 90 (2000) 135–138.
[5] G.A. Vilos, The history of the Papanicolaou smear and the odyssey of George and Andromache Papanicolaou, Obstet. Gynecol. 91 (1998) 479–483.
[6] S.Y. Tan, Y. Tatsumura, George Papanicolaou (1883-1962): discoverer of the Pap smear, Singap. Med. J. 56 (2015) 586–587.
[7] C.R. Stockard, G.N. Papanicolaou, The existence of a typical oestrous cycle in the Guinea-pig--with a study of its histological and physiological changes, Dev. Dyn. 22 (1917).
[8] University of Michigan, Personal/Biographical - Autobiographical and Biographical Notes, 1844 and 1917–1933, University of Michigan Archival Collections - Bentley Library, 2014https://deepblue.lib.umich.edu/handle/2027.42/102891?show=full.
[9] S. Cottrell, The Origins of the Battle Creek Health Reform Movement, Heritage Battle Creek 2009.
[10] Michigan State University. John Harvey Kellogg Papers (Collection Identifier 00013). Michigan State University Archives and Historical Collections. East Lansing, MI. p. http://archives.msu.edu/findaid/013.html.
[11] J.H. Kellogg, Relation of public health to race degeneracy, Am J Public Health (N Y) 4 (1914) 649–663.
[12] G.N. Papnicolaou, H.F. Traut, The diagnostic value of vaginal smears in carcinoma of the uterus, Am. J. Obstet. Gynecol. 42 (1941) 193–224.
[13] H.F. Traut, G.N. Papanicolaou, Cancer of the uterus: the vaginal smear in its diagnosis, Cal West Med 59 (1943) 121–122.
[14] G.N. Papanicolaou, Diagnostic value of exfoliated cells from cancerous tissues, J. Am. Med. Assoc. 131 (1946) 372–378.
[15] J.E. Dunn, J.C. Rowan, C.C. Erickson, E.E. Siegler, Uterine cancer morbidity data; Memphis and Shelby County, Tenn., 1950-51, Public Health Rep. 69 (1954) 269–274.
[16] C. Erickson, Exfoliative cytology in mass screening for uterine Cancer: Memphis and Shelby County, Tennessee. CA, A Cancer Journal for Clinicians 5 (1955) 63–64.
[17] J.E. DUNN, Preliminary findings of the Memphis-Shelby county uterine cancer study and their interpretation, Am J Public Health Nations Health. 48 (1958) 861–873.
[18] W.M. CHRISTOPHERSON, J.E. PARKER, J.C. Drye, Control of cervical cancer. Preliminary report on community program, JAMA 182 (1962) 179–182.
[19] R.T. Javier, J.S. Butel, The history of tumor virology, Cancer Res. 68 (2008) 7693–7706.
[20] P. Rous, A sarcoma of the fowl transmissible by an agent separable from the tumor cells, J. Exp. Med. 13 (1911) 397–411.
[21] P. Rous, J.W. Beard, The progression to carcinoma of virus-induced rabbit papillomas (SHOPE), J. Exp. Med. 62 (1935) 523–548.
[22] H. zur Hausen, W. Meinhof, W. Scheiber, G.W. Bornkamm, Attempts to detect virus-specific DNA in human tumors. I. Nucleic acid hybridizations with complementary RNA of human wart virus, Int. J. Cancer 13 (1974) 650–656.
[23] H. zur Hausen, Papillomaviruses in the causation of human cancers - a brief historical account, Virology 384 (2009) 260–265.
[24] H. zur Hausen, Human papillomaviruses and their possible role in squamous cell carcinomas, Curr. Top. Microbiol. Immunol. 78 (1977) 1–30.
[25] Harald zur Hausen - Biographical. , Nobelprize.org: Nobel Media AB, 2014.
[26] L. Gissmann, M. Boshart, M. Durst, H. Ikenberg, D. Wagner, H. zur Hausen, Presence of human papillomaviruses in genital tumors, J. Investig. Dermatol. 83 (1984) (26s–8s).
[27] J.T. Schiller, D.R. Lowy, Prospects for cervical cancer prevention by human papillomavirus vaccination, Cancer Res. 66 (2006) 10229–10232.
[28] R.K. Gibb, M.G. Martens, The impact of liquid-based cytology in decreasing the incidence of cervical cancer, Rev. Obstet. Gynecol. 4 (2011) S2–S11.
[29] M. Arbyn, C. Bergeron, P. Klinkhamer, P. Martin-Hirsch, A.G. Siebers, J. Bulten, Liquid compared with conventional cervical cytology: a systematic review and meta-analysis, Obstet. Gynecol. 111 (2008) 167–177.
[30] C.J. Roe, K.Z. Hanley, Updates in cervical cytology: the 90-year-long journey from Battle Creek to today, Surg Pathol Clin 11 (2018) 589–599.
[31] Cervical Cancer. , World Health Organization, 2019.
[32] Human Papillomavirus (HPV) and Cervical Cancer. , World Health Organization, 2019.
[33] S. Pimple, G. Mishra, S. Shastri, Global strategies for cervical cancer prevention, Curr Opin Obstet Gynecol 28 (2016) 4–10.