# Prevalence and Genotype Distribution of HPV Types in Women at Risk for Cervical Neoplasia in Israel

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**ABSTRACT:** **Background:** Invasive cervical cancer is caused by human papillomavirus (HPV).

**Objectives:** To describe the prevalence and genotype distribution of HPV types in women at risk for cervical neoplasia.

**Methods:** Our study summarized HPV types detected in 6654 samples that were sent to the serology laboratory from cervical clinics in northern Israel between 2006–2014. The HPV test was performed during investigation of atypical squamous cells of undetermined significance (ASCUS) results on Pap tests or due to complaints suggestive of cervical neoplasia. HPV types were classified as high risk (HPV-HR) and low risk (HPV-LR).

**Results:** Of the samples, 46.4% (3085/6654) were HPV-HR positive. Of women with cervical intraepithelial neoplasia 2-3 (CIN 2-3) or cancer, 292/318 (91.8%) and 137/145 (94.5%), respectively, were HPV-HR positive. HPV 16 and HPV 18 were detected in 11.8% of the total samples and in 48.2% and 64.9% of the women with CIN 2-3 and with cancer, respectively. HPV was negative in 8/145 (5.5%) and 26/318 (8.2%) of women with cervical cancer and CIN 2-3, respectively.

**Conclusions:** This study shows the prevalence of HPV types in women at risk for cervical neoplasia. The sensitivity of all HPV types for CIN 2-3 and cervical cancer was 91.8% and 94.5%, respectively; and of HPV-HR types, 89% and 92.4%, respectively. Triage of HPV-HR types should be considered in women with ASCUS because HPV-HR types were discovered in only 36.7%. The distribution of HPV types in our population is similar to that reported for other developed countries.

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**KEY WORDS:** human papillomavirus (HPV), cervical carcinoma, atypical squamous cells of undetermined significance (ASCUS), cervical intraepithelial neoplasia 1 (CIN 1), cervical intraepithelial neoplasia 2-3 (CIN 2-3)

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Invasive cervical cancer is caused by human papillomavirus (HPV). HPV is classified as a biologic carcinogen, and HPV infection was reported as detected in 99.9% of cervical cancer cases [1]. In epidemiological studies conducted throughout the world, HPV has been detected in 85–93% of women with cervical cancer [2,3]. HPV 16 and 18 are the most common types and have been reported in 70% of HPV positive cases of cervical cancer, in 50% of cervical intraepithelial neoplasia 2-3 (CIN 2-3), and in 25% of CIN 1 patients [4].

The introduction of the Papanicolau (Pap) smear and organized cervical cytological screening has greatly contributed to decreased mortality by cervical cancer, and is considered the most cost-effective cancer screening test developed [5]. However, cervical cytology has significant drawbacks, including both false positive and false negative results. A number of developed countries are currently examining the possible implementation of HPV screening due to its greater efficiency for women over age 30 years and its provision of 60–70% more protection against cervical cancer compared to Pap-based screening programs [6]. The introduction of vaccines against HPV 16 and HPV 18 and against HPV 6/11/16/18 may potentially change the attitude toward cervical cancer prevention.

The prevalence of cervical cancer in Israel is relatively low (5.6 of 100,000 women), but mortality due to cervical cancer is 2.1 of 100,000 [7], similar to that reported in France and the United Kingdom, 1.8 and 2.0 of 100,000, respectively. A few studies have reported the prevalence of HPV types in cervical cancer or CIN in Israel [8-10] but there are no studies that describe the prevalence of HPV in the general population. In Israel screening is only opportunistic and voluntary; therefore, accessing data of HPV prevalence in the general population is difficult. The present study was conducted to determine the prevalence of HPV types in samples sent to a central laboratory from women at risk of cervical neoplasia in northern Israel. Those cases were investigated because of atypical squamous cells of undetermined significance (ASCUS) results on their Pap test or due to complaints suggestive of cervical neoplasia. The collected data are important to determine the HPV types in the Israeli population, evaluate the benefits of HPV screening, and highlight the limitations of HPV screening.

## PATIENTS AND METHODS

### STUDY POPULATION

Samples for HPV typing (6654) were sent to the central serology laboratory at Carmel Medical Center from cervical clinics in Haifa, northern Israel, and the Sharon area between

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September 2006 and July 2014 from patients belonging to Clalit Health Services, the largest health maintenance organization in Israel. Of these, 4569 (68.7%) samples from the Haifa district were sent from the colposcopy clinics due to one abnormal result of ASCUS in the Pap smear or due to complaints suggestive of cervical pathology, such as postcoital bleeding, vaginal discharge, post-menopausal bleeding, menorrhagia, or findings during a gynecological examination of cervical ectropion or erosion. From 370 women, HPV samples were taken twice during the period of the study. All of those patients were evaluated by colposcopy after application of 5% acetic acid solution. HPV typing was taken, as well as cervical biopsy or endocervical curettage as requested. In addition, either endometrial sampling or large loop excision of the transformation zone (LLETZ) was performed as indicated. Cytological findings were classified according to the Bethesda Classification and cervical results were classified as normal, cervical intraepithelial neoplasia (CIN) 1, CIN 2-3, or cancer. The most severe pathological results from the cervical biopsy or from the LLETZ operation were recorded. All the pathological results of CIN 1, CIN 2-3, and cervical cancer are from the Haifa district.

The HPV types were considered to be in the ASCUS group, but if the final pathological result of investigation was CIN 2-3, the HPV type was also counted in that group. A total of 1039 (15.6%) samples were received and sent from Sharon district, and 1046 (15.7%) samples were received from northern Israel (Afula and Kiryat Shmona). From those samples, we know only the reason for the HPV test (ASCUS, post-coital bleeding, ectropion, or erosion) but we do not have the results of their investigation in the cervical clinic and the final pathological results of the evaluation.

The study protocol was approved by the ethical review committee of the Carmel Medical Center, Haifa, protocol number CMC 88-0069.

**Table 1.** HPV prevalence according to cytology and pathology; proportions of HPV, high risk HPV (HPV-HR) and low risk (HPV-LR) in the entire sample and in subgroups of women with atypical squamous cells of undetermined significance (ASCUS), cervical intraepithelial neoplasia, CIN 1, CIN 2-3, and cervical cancer

| HPV type | Percent of entire sample, n (%) | Percent of ASCUS subgroup, n (%) | Percent of CIN 1 subgroup, n (%) | Percent of CIN 2-3 subgroup, n (%) | Percent of carcinoma subgroup, n (%) |
|---|---|---|---|---|---|
| HPV-HR | 2528 (37.9%) | 812 (36.7%) | 63 (44.6%) | 283 (88.9%) | 134 (92.4%) |
| HPV-LR | 557 (8.3%) | 179 (8.1%) | 16 (11.4%) | 9 (2.9%) | 3 (2.1%) |
| All HPV positive | 3085 (46.4%) | 991 (44.8%) | 79 (56.0%) | 292 (91.8%) | 137 (94.5%) |
| HPV negative | 3569 (53.6%) | 1219 (55.2%) | 62 (44.0%) | 26 (8.2%) | 8 (5.5%) |
| Total | 6654 (100%) | 2210 (100%) | 141 (100%) | 318 (100%) | 145 (100%) |

HPV = human papillomavirus, LR = low risk, HR = high risk, ASCUS = atypical squamous cells of undetermined significance, CIN = cervical intraepithelial neoplasia

### HPV DETECTION AND GENOTYPING

DNA was extracted from cervical swabs (Copan, Italy) using an automated extractor (easyMag, Biomerieux, Belgium) according to the manufacturer's instructions [11,12]. Saline (1.5 ml) was added to the swab. After vortex, 0.5 ml suspension was uploaded on the automatic extractor with 0.2 ml elution. HPV genotype was determined by nested polymerase chain reaction (PCR) [11,12]. 0.05 ml of extracted DNA was subjected to PCR with 0.4 uM of forward and reverse primers, 1.25 mM dNTPs and 0.2 ul of Taq DNA polymerase. Nucleotide sequencing and analysis of genotype was performed by Hylabs (Rehovot, Israel). Samples of an undetermined genotype were analyzed by a reverse hybridization line probe assay (INNO-LiPA HPV Genotyping Extra, Innogenetics N.V., Belgium). These assays enabled detection of 61 HPV types. Twenty types were classified as high risk (HPV-HR):16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 70, 73, 82, 85 and IS 39 [13]. Twenty-two types were classified as low risk (HPV-LR): 6, 11, 32, 40, 42, 43, 44, 54, 55, 61, 62, 64, 71, 72, 74, 81, 83, 84, 87, 89, 91, and CP6108. Nineteen genotypes were described as "other types" (HPV types 5, 7, 10, 20, 30, 34, 41, 43, 65, 69, 71, 74, 83, 84, 87, 91, L1AE2/HPV, ISO039, and JC9710) [13].

### STATISTICAL ANALYSIS

Data analysis was performed using the IBM SPSS statistical package version 22.0 (SPSS Inc., Chicago, IL, USA). Significant differences in groups were assessed by the chi-square test. Differences < 0.001 were considered significant.

## RESULTS

A total of 6654 samples were analyzed from women in the age range of 17–80 years (mean 37.8 years). The most prevalent indication for HPV testing was an ASCUS result on the Pap test (57%). Suspicious complaints or such clinical findings as postcoital bleeding, cervical ectropion, cervical erosions (27.2%), and other abnormal Pap test results were indications for the remaining women (15.8%). Data were analyzed from samples of all women in the study population and not only from those who were HPV positive.

Using the present methodology, we were able to detect a total of 51 HPV genotypes. We were unable to define the genotype in only 21 (1.2%) of the 3085 samples, although they were confirmed HPV positive. The percentage of HPV positive, HPV negative, HPV-HR, and HPV-LR types according to the pathological diagnoses are presented in Table 1. HPV infection was found to be positive in 46.4% of the entire sample.

The most common HPV type in our at-risk population (6654 women) [Table 2] was HPV 16, with an overall prevalence of 10.4% (690 women). The prevalence of HPV 31 was 3.4% (229 women), and of HPV 66, 2.6% (172 women). HPV 18 was detected in only 1.8% (96 women). The prevalence of

each of the other HR genotypes was lower than 2%. Similarly, the prevalence of HPV-LR types was low. Multiple-type infection was the second most prevalent HPV infection in the overall sample, detected in 6.7% (447/6654) of the women. In the CIN 2-3 group it was detected in 7.5% (24/318) of the cases but in only 2% (3/145) of women diagnosed with cervical carcinoma [Table 2]. Closer examination of the 447 samples with multiple infections revealed the presence of at least 36 HPV genotypes. The majority of the HPV types in multiple infections were HPV-HR, reflecting the distribution among samples with a single infection. The most prevalent HPV types were 66, 16, 31, 44, 51, 52, 53, and 45, which were detected in 27.0%, 24.6%, 21.8%, 21.3%, 19.0%, 17.1%, 15.6%, and 12.3% of the samples, respectively. The prevalence of the other types was 10% or lower.

Of 318 women with CIN 2-3, HPV was detected in 91.8% (292/318) and HPV-HR in 88.9% (283/318). Of 145 women diagnosed with cervical cancer, 94.5% (137/145) were positive for any HPV type and 92.4% (134/145) for HPV-HR [Table 1]. Of women with CIN 1 and ASCUS, 56.0% and 44.8% were positive for any HPV type, respectively.

The prevalence of HPV16 was particularly high among women with CIN 2-3 and carcinoma (42.9% and 55.9%, respectively), compared to 23.0% and 13.5% among women with ASCUS and CIN1, respectively. Similarly, for HPV 18, prevalence was considerably higher among women with CIN 1, CIN 2-3, and cancer than among those with ASCUS. HPV 45 was detected in only 1.3% (85/6654) of women in the entire sample and in 0.9% (3/318) of those with CIN2-3 pathology, but in 8.3% (12/145) of women with cervical carcinoma.

In women with ASCUS, prevalence of all HPV types was 44.8 (991/2210) but HPV-HR was detected in only 36.7% (812/2210). HPV-HR prevalence was 44.6% (63/141), 88.9%, and 92.4% among women with CIN 1, CIN 2-3, and carcinoma, respectively. In contrast, the prevalence of HPV-LR was lower: 2.9% (9/318) among women with CIN 2-3 and 2.1% (3/145) among those diagnosed with invasive cancer.

**Table 2.** HPV type according to cytology and pathology; numbers and percentages of HPV types in the entire sample, and among women with ASCUS, CIN 1, CIN 2-3, and carcinoma

| HPV Type | ALL | ASCUS | CIN 1 | CIN 2-3 | Carcinoma |
|---|---|---|---|---|---|
| 16 | 690 (10.4%) | 228 (23.0%) (10.3%) | 19 (13.5%) | 137 (42.9%) | 81 (55.9) |
| 18 | 96 (1.4%) | 30 (1.4%) | 5 (3.5%) | 17 (5.3%) | 13 (9.0%) |
| 26 | 2 (0.1%) | 2 (0.1%) | 0 | 0 | |
| 31 | 229 (3.4%) | 72 (3.3%) | 1 (0.7%) | 31 (9.7%) | 4 (2.8%) |
| 33 | 23 (0.3%) | 8 (0.4%) | 3 (2.1%) | 5 (1.6%) | 4 (2.8%) |
| 35 | 72 (1.1%) | 23 (1.0%) | 1 (0.7%) | 6 (1.9%) | 3 (2.0%) |
| 39 | 56 (0.8%) | 16 (0.7%) | 1 (0.7%) | 8 (2.5%) | 3 (2.0%) |
| 45 | 85 (1.3%) | 20 (0.9%) | 0 | 3 (0.9%) | 12 (8.3%) |
| 51 | 54 (0.8%) | 16 (0.7%) | 4 (2.8%) | 7 (2.2%) | 0 |
| 52 | 69 (1.0%) | 23 (1.0%) | 0 | 5 (1.6%) | 0 |
| 53 | 97 (1.5%) | 30 (1.4%) | 4 (2.8%) | 2 (0.6%) | 0 |
| 56 | 128 (1.9%) | 46 (2.1%) | 3 (2.1%) | 7 (2.2%) | 3 (2.0%) |
| 58 | 73 (1.1%) | 28 (1.3%) | 4 (2.8%) | 9 (2.8%) | 1 (0.7%) |
| 59 | 59 (0.9%) | 29 (1.3%) | 3 (2.1%) | 5 (1.6%) | 2 (1.4%) |
| 66 | 172 (2.6%) | 70 (3.2%) | 4 (2.8%) | 8 (2.5%) | 2 (1.4%) |
| 67 | 53 (0.8%) | 17 (0.8%) | 1 (0.7%) | 3 (0.9%) | 0 |
| 68 | 34 (0.5%) | 10 (1.3(2.0%)0%) | 1 (1.3%) | 3 (1.0%) | 0 |
| 70 | 45 (0.7%) | 18 (0.8%) | 1 (0.7%) | 1 (0.3%) | 0 |
| 73 | 40 (0.6%) | 3 (0.1%) | 1 (0.7%) | 2 (0.6%) | 2 (1.4%) |
| 82 | 4 (0.1%) | 0 | 1 (0.7%) | 0 | 1 (0.7%) |
| Multiple Types | 447 (6.7%) | 123 (5.6%) | 6 (4.3%) | 24 (7.5%) | 3 (2.0%) |
| 6 | 112 (1.7%) | 48 (2.2%) | 6 (4.3%) | 6 (1.9%) | |
| 11 | 28 (0.4%) | 16 (0.7%) | 0 | 0 | |
| 32 | 4 (0.1%) | 2 (0.1%) | 0 | 0 | |
| 40 | 4 (0.1%) | 1 (0.1%) | 0 | 0 | |
| 42 | 55 (0.8%) | 27 (1.2%) | 4 (2.8%) | 1 (0.3%) | |
| 44 | 10(0.2%) | 1 (0.1%) | 0 | 0 | |
| 54 | 99 (1.5%) | 43 (1.9%) | 1 (0.7%) | 1 (0.3%) | 1 (0.7%) |
| 55 | 10 (0.2%) | 4 (0.2%) | 0 | 0 | |
| 61 | 8 (0.1%) | 0 | 0 | 0 | |
| 62 | 45 (0.7%) | 8 (0.4%) | 0 | 0 | 1 (0.7%) |
| 64 | 2 (0.01%) | 1 (0.1%) | 0 | 0 | |
| 72 | 5 (0.1%) | 2 (0.1%) | 0 | 0 | |
| CP6108 | 4 (0.4%) | 8 (0.4%) | 0 | 1 (0.3%) | |
| Other HPV Types | 171 (26.0%) | 18 (1.8%) | 5 (6.3%) | 0 | 1 (0.7%) |
| All HPV positive | 3085 (46.4%) | 991 (44.8%) | 79 (56.0%) | 292 (91.8%) | 137 (94.5%) |
| HPV negative | 3569 (53.6%) | 1219 (55.2%) | 62 (43.0%) | 26 (8.1%) | 8 (5.5%) |
| TOTAL | 6654 | 2210 | 141 | 318 | 145 |

HPV = human papillomavirus, ASCUS = atypical squamous cells of undetermined significance, CIN = cervical intraepithelial neoplasia

## DISCUSSION

This comprehensive study represents all HPV genotypes (low risk and high risk) detected in women at high risk for cervical neoplasia in the north and Sharon district of Israel using molecular diagnosis of HPV. Reliable data on the incidence of HPV types is important for determining the types that should be included in a screening program, as well as for evaluating the efficiency of the existing vaccine against HPV 16 and HPV 18, or against HPV 6, HPV 11, HPV 16, and HPV 18, or future vaccines against nine HPV types (HPV 6, HPV 11, HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52, and HPV 58).

The methodology used in this study of nested PCR followed by sequencing provides reliable results and enables the identification of 61 genital-associated HPV genotypes. Sequencing enables determining the genotype only in infections with a single genotype. Therefore, we used the hybridization method (INNO-LiPA, Innogenetics N.V., Belgium) to identify HPV

types that are involved in multiple infections. This study demonstrates similar prevalence of HPV types in cervical pathology in Israel as well as other developed countries [13]. The dominant type was HPV16.

In the present study, multiple HPV infection was the second most common result overall, although occurrence was only 2% in women with cervical cancer. Although the majority of the multiple infection specimens harbored at least one high-risk type, the prevalence of multiple HPV types in malignant specimens was low. This finding is similar to that of a study from Europe in which multiple HPV infections occurred in 17.2–19.4% of high-grade CIN and in 2.5–4.4% of invasive cervical cancer [14,15].

Of women who were investigated due to ASCUS results on Pap tests, 36.7% (812/2210) were positive for HPV-HR types (including multiple types). These data are similar to findings of U.S. women, in which a hybrid capture test showed HPV-HR positivity in 44% of the women investigated due to ASCUS [16]. Those findings support HPV testing as the preferred first step in ASCUS investigation because it can save repeated Pap smear, colposcopy, and cervical biopsy from 63.3% of the ASCUS population.

In women with CIN 1 diagnosis, HPV-HR types (including multiple types) were detected in 44.6% (63/141), while HPV was negative in 44.0% (62/141). Despite the small number of women in this group, this finding suggests that HPV types might be a factor considered in deciding between continuous observation and surgical treatment for women with persistent CIN1 pathology. More data are needed to determine the optimal role of HPV typing in the management of women with CIN1.

In this study, HPV 16 and HPV 18 were detected in 42.9% and 5.3% of women with CIN 2-3, respectively, and in 55.9% and 9.0%, respectively, of women with cervical cancer. These proportions are similar to the numbers from the EDITH study from France, in which single type infection with HPV 16 and HPV 18 were detected in 40.4% and 8.3%, respectively of CIN 2-3 lesions, and in 53.3% and 7.6% of women with cervical cancer [17,18].

A meta-analysis conducted by Smith et al. [19] of HPV types in high-grade squamous intraepithelial lesions and invasive cancer in 9494 women found HPV 16, HPV 18, HPV 31, HPV 45, and HPV 66 in 55.2%, 12.8%, 3.8%, 4.6%, and 0.4% of women with cervical cancer and in 45.3%, 6.9%, 8.6 %, 2.3%, and 1.9% of women with high-grade squamous intraepithelial lesions [19]. In our population, the prevalence of HPV 16, HPV 18 and HPV 31 in women with cervical cancer was similar to that of the meta-analysis: 55.9 %, 9.0%, and 2.8%; however, HPV 45 and HPV 66 were more common and detected in 8.3% and 1.4% of samples, respectively. In women with CIN 2-3 we found HPV 16, HPV 18, HPV 31, HPV 45, and HPV 66 in 42.9%, 5.3%, 9.7%, 0.9%, and 2.5%. These results are similar to those from Smith's meta-analysis.

Data from Israel published by Shavit and colleagues [7], showed that HPV 16 was detected in 46.5% of women with CIN 2-3 and in 48.6% of women with invasive cervical cancer. In another study by Bassal and co-authors [10], HPV types were found in 89.3% and 85% from women with cervical cancer and CIN 3, respectively.

In our study, in women with cervical cancer and CIN2-3, HPV was negative in 5.5% (8/144) and 8.2% (26/318) of the patients. These data should point to the limitations of HPV screening. Nine women (2.8%) with CIN 2-3 and seven (2.1%) with cervical cancer had HPV-LR.

HPV-LR types rarely cause invasive cancer but the risk of invasive cancer among women with CIN 2-3 and HPV-LR is not known. Therefore, more data are needed to determine if these women should be treated differently from women with CIN 2-3 and HPV-HR.

Cervical cancer is a neoplasia that is almost completely preventable. The role of HPV in this cancer highlights the importance of HPV detection. DNA testing of high-risk HPV types in different formats has been validated. An extensive Swedish study [20] concluded that screening by means of combined HPV and Pap tests versus cytological screening alone significantly reduced the incidence of CIN 2-3 in women in their fourth decade of life. A meta-analysis by Ronco et al. [6] based on four randomized trials comparing cytology screening to HPV screening found that HPV-based screening provides 60–70% greater protection against invasive cervical carcinomas compared to cytology. Data of large-scale randomized trials support initiation of HPV-based screening from age 30 years.

We detected a large number of high-risk HPV types in a high risk population, but only 16 HPV-HR types were presented in women diagnosed with cervical cancer. An HPV vaccine could have prevented 64.9% of the cervical cancer and 48.2% of the CIN 2-3 lesions detected in the current study. However, the introduction of any new treatment or new screening test requires measuring effectiveness based on data of the local population. This study provides baseline information on the HPV distribution in a high-risk population in Israel. These results may contribute to the planning of cervical cancer prevention and screening programs in this country. A large national multi-center study should be performed to obtain a more conclusive evaluation of the prevalence of HPV types in the general population of women in Israel.

The strength of the current study is its large size. It is the largest investigation of women with high risk for cervical dysplasia in Israel. Since we examined HPV-LR, as well as HPV-HR types, the sensitivity to detect CIN 2-3 and cervical cancer was relatively high: 91.8% and 94.5% respectively. These data raise the question as to whether HPV-LR types should be included in HPV screening to increase HPV screening sensitivity. The lack of detection of HPV types in 8.1% (26/318) and 5.5% (8/145) of women with CIN 2-3 and cervical cancer, respectively, dem-

onstrates limitations of an HPV screening program that may be implemented in the future.

The limitations of this study are that being a referral laboratory, we received HPV tests from a few regions in Israel. We do not have the details of the investigation and the final pathological results of all the study populations. We are also missing demographic characteristics of our population.

We need more data about HPV types in women with low-grade squamous intraepithelial lesions and CIN 1, to determine the value of HPV typing in investigations or treatments of those women, and cost effective studies should be performed to decide what is the best way to investigate women with ASCUS results on the pap test? We also need more data on women with CIN 2-3 lesions who have HPV-LR types to evaluate the risk for those women to progress to invasive cancer.

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## Capsule

### An antisensible approach to target *KRAS*

Mutations that cause activation of the *KRAS* oncogene are common in human cancer, including treatment-resistant tumor types such as lung and pancreatic cancer. *KRAS* is notoriously difficult to target with small molecules. To overcome this issue, Ross et al. turned to genetic technology to develop an antisense oligonucleotide-based therapy for inhibiting *KRAS*. The antisense oligonucleotide was chemically modified to allow systemic delivery through subcutaneous injection, avoiding the need for a specialized delivery vehicle. The authors tested the efficacy of this therapy in multiple mouse models of non-small cell lung cancer and evaluated its safety in primates, demonstrating its potential suitability for translation to humans.

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Eitan Israeli

**"Freedom makes a huge requirement of every human being. With freedom comes responsibility. For the person who is unwilling to grow up, the person who does not carry his own weight, this is a frightening prospect"**

Eleanor Roosevelt, (1884–1962), American politician, diplomat, and activist. Wife of former U.S. President Franklin D. Roosevelt. Served as United States delegate to the United Nations General Assembly from 1945 to 1952